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(54) Title: MAPCAXS AS MODIFIERS OF THE APC AND AXIN PATHWAYS AND METHODS OF USE

(57) Abstract: Human MAPCAX genes are identified as modulators of the APC and axin pathways, and thus are therapeutic targets for disorders associated with defective APC and axin function. Methods for identifying modulators of APC and axin, comprising screening for agents that modulate the activity of MAPCAX are provided.

MAPCAXs AS MODIFIERS OF THE APC AND AXIN PATHWAYS AND METHODS OF USE

REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. provisional patent applications 60/443,484 filed 1/29/2003, 60/447,358 filed 2/11/2003, 60/461,789 filed 4/10/2003, 60/470,684 filed 5/14/2003, and 60/479,650 filed 6/19/2003. The contents of the prior applications are hereby incorporated in their entirety.

BACKGROUND OF THE INVENTION

Deregulation of beta-catenin signaling is a frequent and early event in the development of a variety of human tumors, including colon cancer, melanoma, ovarian cancer, and prostate cancer. Activation of beta-catenin signaling can occur in tumor cells by loss-of-function mutations in the tumor suppressor genes APC (adenomatus polyposis coli protein) or Axin, as well as by gain-of-function mutations in the oncogene beta-catenin itself. APC, Axin, and beta-catenin normally bind to each other, as well as to the serine/threonine kinase GSK3-beta. Assembly of this degradation complex allows GSK3-beta to phosphorylate beta-catenin, which leads to beta-catenin ubiquitination and degradation by the proteasome. In the absence of APC or Axin activity, beta-catenin protein becomes stabilized and accumulates in the nucleus where it acts as a transcriptional co-activator with TCF for the induction of target genes, including the cell cycle regulators cyclin D1 and c-Myc.

The *C. elegans* gene *pry-1* is the structural and functional ortholog of vertebrate Axin (Korswagen HC et al. (2002) Genes Dev. 16:1291-302). PRY-1 is predicted to contain conserved RGS and DIX domains that, in Axin, bind APC and Dishevelled, respectively. Overexpression of the *C. elegans pry-1* gene in zebrafish can fully rescue the mutant phenotype of *masterblind*, the zebrafish Axin1 mutation. *pry-1* loss-of-function mutations produce several phenotypes that appear to result from increased beta-catenin signaling (Gleason JE et al. (2002) Genes Dev. 16:1281-90; Korswagen et al., *supra*). We find that the temperature-sensitive, reduction-of-function *pry-1* mutant *mu38* grown at 25°C produces a multivulva (Muv) phenotype in which approximately 30% of animals are induced to form ectopic vulvae. The *pry-1* Muv mutant phenotype is suppressed by RNAi-mediated inactivation the beta-catenin ortholog *bar-1* and the TCF ortholog *pop-1*. The Muv phenotype can also be generated by gain-of-function mutations

in *bar-1*/beta-catenin that eliminate the consensus GSK3-beta phosphorylation sites and are predicted to prevent Axin-mediated degradation of BAR-1.

The *C. elegans* gene product APR-1 shows significant structural similarity to human APC and can bind to both BAR-1/beta-catenin and PRY-1/Axin (Rocheleau et al. (1997), Cell, Vol. 90, 707–716; Natarajan et al. (2001), Genetics, Vol. 159, 159-172; Korswagen et al., *supra*).

The ability to manipulate the genomes of model organisms such as *C. elegans* provides a powerful means to analyze biochemical processes that, due to significant evolutionary conservation, have direct relevance to more complex vertebrate organisms. Due to a high level of gene and pathway conservation, the strong similarity of cellular processes, and the functional conservation of genes between these model organisms and mammals, identification of the involvement of novel genes in particular pathways and their functions in such model organisms can directly contribute to the understanding of the correlative pathways and methods of modulating them in mammals (see, for example, Dulubova I, et al, J Neurochem 2001 Apr;77(1):229-38; Cai T, et al., Diabetologia 2001 Jan;44(1):81-8; Pasquinelli AE, et al., Nature. 2000 Nov 2;408(6808):37-8; Ivanov IP, et al., EMBO J 2000 Apr 17;19(8):1907-17; Vajo Z et al., Mamm Genome 1999 Oct;10(10):1000-4). For example, a genetic screen can be carried out in an invertebrate model organism having underexpression (e.g. knockout) or overexpression of a gene (referred to as a "genetic entry point") that yields a visible phenotype. Additional genes are mutated in a random or targeted manner. When a gene mutation changes the original phenotype caused by the mutation in the genetic entry point, the gene is identified as a "modifier" involved in the same or overlapping pathway as the genetic entry point. When the genetic entry point is an ortholog of a human gene implicated in a disease pathway, such as APC and axin, modifier genes can be identified that may be attractive candidate targets for novel therapeutics.

All references cited herein, including patents, patent applications, publications, and sequence information in referenced Genbank identifier numbers, are incorporated herein in their entireties.

SUMMARY OF THE INVENTION

We have discovered genes that modify the APC and axin pathways in *C. elegans*, and identified their human orthologs, hereinafter referred to as modifier of APC and Axin (MAPCAX). The invention provides methods for utilizing these APC and axin modifier

genes and polypeptides to identify MAPCAX-modulating agents that are candidate therapeutic agents that can be used in the treatment of disorders associated with defective or impaired APC and axin function and/or MAPCAX function. Preferred MAPCAX-modulating agents specifically bind to MAPCAX polypeptides and restore APC and axin function. Other preferred MAPCAX-modulating agents are nucleic acid modulators such as antisense oligomers and RNAi that repress MAPCAX gene expression or product activity by, for example, binding to and inhibiting the respective nucleic acid (i.e. DNA or mRNA).

MAPCAX modulating agents may be evaluated by any convenient *in vitro* or *in vivo* assay for molecular interaction with a MAPCAX polypeptide or nucleic acid. In one embodiment, candidate MAPCAX modulating agents are tested with an assay system comprising a MAPCAX polypeptide or nucleic acid. Agents that produce a change in the activity of the assay system relative to controls are identified as candidate APC and axin modulating agents. The assay system may be cell-based or cell-free. MAPCAX-modulating agents include MAPCAX related proteins (e.g. dominant negative mutants, and biotherapeutics); MAPCAX -specific antibodies; MAPCAX -specific antisense oligomers and other nucleic acid modulators; and chemical agents that specifically bind to or interact with MAPCAX or compete with MAPCAX binding partner (e.g. by binding to a MAPCAX binding partner). In one specific embodiment, a small molecule modulator is identified using a binding assay. In specific embodiments, the screening assay system is selected from an apoptosis assay, a cell proliferation assay, an angiogenesis assay, and a hypoxic induction assay.

In another embodiment, candidate APC and axin pathways modulating agents are further tested using a second assay system that detects changes in the APC and axin pathways, such as angiogenic, apoptotic, or cell proliferation changes produced by the originally identified candidate agent or an agent derived from the original agent. The second assay system may use cultured cells or non-human animals. In specific embodiments, the secondary assay system uses non-human animals, including animals predetermined to have a disease or disorder implicating the APC and axin pathways, such as an angiogenic, apoptotic, or cell proliferation disorder (e.g. cancer).

The invention further provides methods for modulating the MAPCAX function and/or the APC and axin pathways in a mammalian cell by contacting the mammalian cell with an agent that specifically binds a MAPCAX polypeptide or nucleic acid. The agent may be a small molecule modulator, a nucleic acid modulator, or an antibody and may be

administered to a mammalian animal predetermined to have a pathology associated with the APC and axin pathways.

DETAILED DESCRIPTION OF THE INVENTION

Genetic screens were designed to identify modifiers of the axin and APC pathway in *C. elegans*. The function of *apr-1* was depleted by RNAi in a *pry-1* hypomorphic allele *mu38*. Various specific genes were then silenced by RNA inhibition (RNAi). Methods for using RNAi to silence genes in *C. elegans* are known in the art (Fire A, et al., 1998 Nature 391:806-811; Fire, A. Trends Genet. 15, 358-363 (1999); WO9932619). Genes causing altered phenotypes in the worms were identified as modifiers of the APC and axin pathways. Modifiers of particular interest, were identified followed by identification of their orthologs. Accordingly, vertebrate orthologs of these modifiers, and preferably the human orthologs, MAPCAX genes (i.e., nucleic acids and polypeptides) are attractive drug targets for the treatment of pathologies associated with a defective APC and axin signaling pathway, such as cancer. Table 1 (Example II) lists the modifiers and their orthologs.

In vitro and in vivo methods of assessing MAPCAX function are provided herein. Modulation of the MAPCAX or their respective binding partners is useful for understanding the association of the APC and axin pathways and their members in normal and disease conditions and for developing diagnostics and therapeutic modalities for APC and axin related pathologies. MAPCAX-modulating agents that act by inhibiting or enhancing MAPCAX expression, directly or indirectly, for example, by affecting a MAPCAX function such as enzymatic (e.g., catalytic) or binding activity, can be identified using methods provided herein. MAPCAX modulating agents are useful in diagnosis, therapy and pharmaceutical development.

Nucleic acids and polypeptides of the invention

Sequences related to MAPCAX nucleic acids and polypeptides that can be used in the invention are disclosed in Genbank (referenced by Genbank identifier (GI) or RefSeq number), shown in Table 1 and in the sequence listing.

The term "MAPCAX polypeptide" refers to a full-length MAPCAX protein or a functionally active fragment or derivative thereof. A "functionally active" MAPCAX fragment or derivative exhibits one or more functional activities associated with a full-length, wild-type MAPCAX protein, such as antigenic or immunogenic activity,

enzymatic activity, ability to bind natural cellular substrates, etc. The functional activity of MAPCAX proteins, derivatives and fragments can be assayed by various methods known to one skilled in the art (Current Protocols in Protein Science (1998) Coligan *et al.*, eds., John Wiley & Sons, Inc., Somerset, New Jersey) and as further discussed below. In one embodiment, a functionally active MAPCAX polypeptide is a MAPCAX derivative capable of rescuing defective endogenous MAPCAX activity, such as in cell based or animal assays; the rescuing derivative may be from the same or a different species. For purposes herein, functionally active fragments also include those fragments that comprise one or more structural domains of a MAPCAX, such as a binding domain. Protein domains can be identified using the PFAM program (Bateman A., et al., Nucleic Acids Res, 1999, 27:260-2). Methods for obtaining MAPCAX polypeptides are also further described below. In some embodiments, preferred fragments are functionally active, domain-containing fragments comprising at least 25 contiguous amino acids, preferably at least 50, more preferably 75, and most preferably at least 100 contiguous amino acids of a MAPCAX. In further preferred embodiments, the fragment comprises the entire functionally active domain.

The term "MAPCAX nucleic acid" refers to a DNA or RNA molecule that encodes a MAPCAX polypeptide. Preferably, the MAPCAX polypeptide or nucleic acid or fragment thereof is from a human, but can also be an ortholog, or derivative thereof with at least 70% sequence identity, preferably at least 80%, more preferably 85%, still more preferably 90%, and most preferably at least 95% sequence identity with human MAPCAX. Methods of identifying orthlogs are known in the art. Normally, orthologs in different species retain the same function, due to presence of one or more protein motifs and/or 3-dimensional structures. Orthologs are generally identified by sequence homology analysis, such as BLAST analysis, usually using protein bait sequences. Sequences are assigned as a potential ortholog if the best hit sequence from the forward BLAST result retrieves the original query sequence in the reverse BLAST (Huynen MA and Bork P, Proc Natl Acad Sci (1998) 95:5849-5856; Huynen MA *et al.*, Genome Research (2000) 10:1204-1210). Programs for multiple sequence alignment, such as CLUSTAL (Thompson JD et al, 1994, Nucleic Acids Res 22:4673-4680) may be used to highlight conserved regions and/or residues of orthologous proteins and to generate phylogenetic trees. In a phylogenetic tree representing multiple homologous sequences from diverse species (e.g., retrieved through BLAST analysis), orthologous sequences from two species generally appear closest on the tree with respect to all other sequences from these two

species. Structural threading or other analysis of protein folding (e.g., using software by ProCeryon, Biosciences, Salzburg, Austria) may also identify potential orthologs. In evolution, when a gene duplication event follows speciation, a single gene in one species, such as *C. elegans*, may correspond to multiple genes (paralogs) in another, such as human. As used herein, the term "orthologs" encompasses paralogs. As used herein, "percent (%) sequence identity" with respect to a subject sequence, or a specified portion of a subject sequence, is defined as the percentage of nucleotides or amino acids in the candidate derivative sequence identical with the nucleotides or amino acids in the subject sequence (or specified portion thereof), after aligning the sequences and introducing gaps, if necessary to achieve the maximum percent sequence identity, as generated by the program WU-BLAST-2.0a19 (Altschul *et al.*, J. Mol. Biol. (1997) 215:403-410) with all the search parameters set to default values. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched. A % identity value is determined by the number of matching identical nucleotides or amino acids divided by the sequence length for which the percent identity is being reported. "Percent (%) amino acid sequence similarity" is determined by doing the same calculation as for determining % amino acid sequence identity, but including conservative amino acid substitutions in addition to identical amino acids in the computation.

A conservative amino acid substitution is one in which an amino acid is substituted for another amino acid having similar properties such that the folding or activity of the protein is not significantly affected. Aromatic amino acids that can be substituted for each other are phenylalanine, tryptophan, and tyrosine; interchangeable hydrophobic amino acids are leucine, isoleucine, methionine, and valine; interchangeable polar amino acids are glutamine and asparagine; interchangeable basic amino acids are arginine, lysine and histidine; interchangeable acidic amino acids are aspartic acid and glutamic acid; and interchangeable small amino acids are alanine, serine, threonine, cysteine and glycine.

Alternatively, an alignment for nucleic acid sequences is provided by the local homology algorithm of Smith and Waterman (Smith and Waterman, 1981, Advances in Applied Mathematics 2:482-489; database: European Bioinformatics Institute; Smith and Waterman, 1981, J. of Molec.Biol., 147:195-197; Nicholas et al., 1998, "A Tutorial on Searching Sequence Databases and Sequence Scoring Methods" (www.psc.edu) and references cited therein.; W.R. Pearson, 1991, Genomics 11:635-650). This algorithm can

be applied to amino acid sequences by using the scoring matrix developed by Dayhoff (Dayhoff: Atlas of Protein Sequences and Structure, M. O. Dayhoff ed., 5 suppl. 3:353-358, National Biomedical Research Foundation, Washington, D.C., USA), and normalized by Gribskov (Gribskov 1986 Nucl. Acids Res. 14(6):6745-6763). The Smith-Waterman algorithm may be employed where default parameters are used for scoring (for example, gap open penalty of 12, gap extension penalty of two). From the data generated, the "Match" value reflects "sequence identity."

Derivative nucleic acid molecules of the subject nucleic acid molecules include sequences that hybridize to the nucleic acid sequence of a MAPCAX. The stringency of hybridization can be controlled by temperature, ionic strength, pH, and the presence of denaturing agents such as formamide during hybridization and washing. Conditions routinely used are set out in readily available procedure texts (*e.g.*, Current Protocol in Molecular Biology, Vol. 1, Chap. 2.10, John Wiley & Sons, Publishers (1994); Sambrook *et al.*, Molecular Cloning, Cold Spring Harbor (1989)). In some embodiments, a nucleic acid molecule of the invention is capable of hybridizing to a nucleic acid molecule containing the nucleotide sequence of a MAPCAX under high stringency hybridization conditions that are: prehybridization of filters containing nucleic acid for 8 hours to overnight at 65° C in a solution comprising 6X single strength citrate (SSC) (1X SSC is 0.15 M NaCl, 0.015 M Na citrate; pH 7.0), 5X Denhardt's solution, 0.05% sodium pyrophosphate and 100 μg/ml herring sperm DNA; hybridization for 18-20 hours at 65° C in a solution containing 6X SSC, 1X Denhardt's solution, 100 μg/ml yeast tRNA and 0.05% sodium pyrophosphate; and washing of filters at 65° C for 1h in a solution containing 0.1X SSC and 0.1% SDS (sodium dodecyl sulfate).

In other embodiments, moderately stringent hybridization conditions are used that are: pretreatment of filters containing nucleic acid for 6 h at 40° C in a solution containing 35% formamide, 5X SSC, 50 mM Tris-HCl (pH7.5), 5mM EDTA, 0.1% PVP, 0.1% Ficoll, 1% BSA, and 500 μg/ml denatured salmon sperm DNA; hybridization for 18-20h at 40° C in a solution containing 35% formamide, 5X SSC, 50 mM Tris-HCl (pH7.5), 5mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 μg/ml salmon sperm DNA, and 10% (wt/vol) dextran sulfate; followed by washing twice for 1 hour at 55° C in a solution containing 2X SSC and 0.1% SDS.

Alternatively, low stringency conditions can be used that are: incubation for 8 hours to overnight at 37° C in a solution comprising 20% formamide, 5 x SSC, 50 mM sodium phosphate (pH 7.6), 5X Denhardt's solution, 10% dextran sulfate, and 20 μg/ml

denatured sheared salmon sperm DNA; hybridization in the same buffer for 18 to 20 hours; and washing of filters in 1 x SSC at about 37° C for 1 hour.

Isolation, Production, Expression, and Mis-expression of MAPCAX Nucleic Acids and Polypeptides

MAPCAX nucleic acids and polypeptides are useful for identifying and testing agents that modulate MAPCAX function and for other applications related to the involvement of MAPCAX in the APC and axin pathways. MAPCAX nucleic acids and derivatives and orthologs thereof may be obtained using any available method. For instance, techniques for isolating cDNA or genomic DNA sequences of interest by screening DNA libraries or by using polymerase chain reaction (PCR) are well known in the art. In general, the particular use for the protein will dictate the particulars of expression, production, and purification methods. For instance, production of proteins for use in screening for modulating agents may require methods that preserve specific biological activities of these proteins, whereas production of proteins for antibody generation may require structural integrity of particular epitopes. Expression of proteins to be purified for screening or antibody production may require the addition of specific tags (*e.g.*, generation of fusion proteins). Overexpression of a MAPCAX protein for assays used to assess MAPCAX function, such as involvement in cell cycle regulation or hypoxic response, may require expression in eukaryotic cell lines capable of these cellular activities. Techniques for the expression, production, and purification of proteins are well known in the art; any suitable means therefore may be used (e.g., Higgins SJ and Hames BD (eds.) Protein Expression: A Practical Approach, Oxford University Press Inc., New York 1999; Stanbury PF et al., Principles of Fermentation Technology, 2nd edition, Elsevier Science, New York, 1995; Doonan S (ed.) Protein Purification Protocols, Humana Press, New Jersey, 1996; Coligan JE et al, Current Protocols in Protein Science (eds.), 1999, John Wiley & Sons, New York). In particular embodiments, recombinant MAPCAX is expressed in a cell line known to have defective APC or axin function. The recombinant cells are used in cell-based screening assay systems of the invention, as described further below.

The nucleotide sequence encoding a MAPCAX polypeptide can be inserted into any appropriate expression vector. The necessary transcriptional and translational signals, including promoter/enhancer element, can derive from the native MAPCAX gene and/or its flanking regions or can be heterologous. A variety of host-vector expression systems

may be utilized, such as mammalian cell systems infected with virus (*e.g.* vaccinia virus, adenovirus, *etc.*); insect cell systems infected with virus (*e.g.* baculovirus); microorganisms such as yeast containing yeast vectors, or bacteria transformed with bacteriophage, plasmid, or cosmid DNA. An isolated host cell strain that modulates the expression of, modifies, and/or specifically processes the gene product may be used.

To detect expression of the MAPCAX gene product, the expression vector can comprise a promoter operably linked to a MAPCAX gene nucleic acid, one or more origins of replication, and, one or more selectable markers (*e.g.* thymidine kinase activity, resistance to antibiotics, *etc.*). Alternatively, recombinant expression vectors can be identified by assaying for the expression of the MAPCAX gene product based on the physical or functional properties of the MAPCAX protein in *in vitro* assay systems (*e.g.* immunoassays).

The MAPCAX protein, fragment, or derivative may be optionally expressed as a fusion, or chimeric protein product (i.e. it is joined via a peptide bond to a heterologous protein sequence of a different protein), for example to facilitate purification or detection. A chimeric product can be made by ligating the appropriate nucleic acid sequences encoding the desired amino acid sequences to each other using standard methods and expressing the chimeric product. A chimeric product may also be made by protein synthetic techniques, *e.g.* by use of a peptide synthesizer (Hunkapiller *et al.*, Nature (1984) 310:105-111).

Once a recombinant cell that expresses the MAPCAX gene sequence is identified, the gene product can be isolated and purified using standard methods (*e.g.* ion exchange, affinity, and gel exclusion chromatography; centrifugation; differential solubility; electrophoresis). Alternatively, native MAPCAX proteins can be purified from natural sources, by standard methods (*e.g.* immunoaffinity purification). Once a protein is obtained, it may be quantified and its activity measured by appropriate methods, such as immunoassay, bioassay, or other measurements of physical properties, such as crystallography.

The methods of this invention may also use cells that have been engineered for altered expression (mis-expression) of MAPCAX or other genes associated with the APC and axin pathways. As used herein, mis-expression encompasses ectopic expression, over-expression, under-expression, and non-expression (*e.g.* by gene knock-out or blocking expression that would otherwise normally occur).

Genetically modified animals

Animal models that have been genetically modified to alter MAPCAX expression may be used in *in vivo* assays to test for activity of a candidate APC and axin modulating agent, or to further assess the role of MAPCAX in a APC and axin pathways process such as apoptosis or cell proliferation. Preferably, the altered MAPCAX expression results in a detectable phenotype, such as decreased or increased levels of cell proliferation, angiogenesis, or apoptosis compared to control animals having normal MAPCAX expression. The genetically modified animal may additionally have altered APC and axin expression (e.g. APC and axin knockout). Preferred genetically modified animals are mammals such as primates, rodents (preferably mice or rats), among others. Preferred non-mammalian species include zebrafish, *C. elegans*, and *Drosophila*. Preferred genetically modified animals are transgenic animals having a heterologous nucleic acid sequence present as an extrachromosomal element in a portion of its cells, i.e. mosaic animals (see, for example, techniques described by Jakobovits, 1994, Curr. Biol. 4:761-763.) or stably integrated into its germ line DNA (i.e., in the genomic sequence of most or all of its cells). Heterologous nucleic acid is introduced into the germ line of such transgenic animals by genetic manipulation of, for example, embryos or embryonic stem cells of the host animal.

Methods of making transgenic animals are well-known in the art (for transgenic mice see Brinster et al., Proc. Nat. Acad. Sci. USA 82: 4438-4442 (1985), U.S. Pat. Nos. 4,736,866 and 4,870,009, both by Leder et al., U.S. Pat. No. 4,873,191 by Wagner et al., and Hogan, B., Manipulating the Mouse Embryo, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1986); for particle bombardment see U.S. Pat. No., 4,945,050, by Sandford *et al.*; for transgenic *Drosophila* see Rubin and Spradling, Science (1982) 218:348-53 and U.S. Pat. No. 4,670,388; for transgenic insects see Berghammer A.J. *et al.*, A Universal Marker for Transgenic Insects (1999) Nature 402:370-371; for transgenic Zebrafish see Lin S., Transgenic Zebrafish, Methods Mol Biol. (2000);136:375-3830); for microinjection procedures for fish, amphibian eggs and birds see Houdebine and Chourrout, Experientia (1991) 47:897-905; for transgenic rats see Hammer *et al.*, Cell (1990) 63:1099-1112; and for culturing of embryonic stem (ES) cells and the subsequent production of transgenic animals by the introduction of DNA into ES cells using methods such as electroporation, calcium phosphate/DNA precipitation and direct injection see, e.g., Teratocarcinomas and Embryonic Stem Cells, A Practical Approach, E. J. Robertson, ed., IRL Press (1987)). Clones of the nonhuman transgenic animals can be produced

according to available methods (see Wilmut, I. *et al.* (1997) Nature 385:810-813; and PCT International Publication Nos. WO 97/07668 and WO 97/07669).

In one embodiment, the transgenic animal is a "knock-out" animal having a heterozygous or homozygous alteration in the sequence of an endogenous MAPCAX gene that results in a decrease of MAPCAX function, preferably such that MAPCAX expression is undetectable or insignificant. Knock-out animals are typically generated by homologous recombination with a vector comprising a transgene having at least a portion of the gene to be knocked out. Typically a deletion, addition or substitution has been introduced into the transgene to functionally disrupt it. The transgene can be a human gene (e.g., from a human genomic clone) but more preferably is an ortholog of the human gene derived from the transgenic host species. For example, a mouse MAPCAX gene is used to construct a homologous recombination vector suitable for altering an endogenous MAPCAX gene in the mouse genome. Detailed methodologies for homologous recombination in mice are available (see Capecchi, Science (1989) 244:1288-1292; Joyner *et al.*, Nature (1989) 338:153-156). Procedures for the production of non-rodent transgenic mammals and other animals are also available (Houdebine and Chourrout, *supra*; Pursel *et al.*, Science (1989) 244:1281-1288; Simms *et al.*, Bio/Technology (1988) 6:179-183). In a preferred embodiment, knock-out animals, such as mice harboring a knockout of a specific gene, may be used to produce antibodies against the human counterpart of the gene that has been knocked out (Claesson MH et al., (1994) Scan J Immunol 40:257-264; Declerck PJ et al., (1995) J Biol Chem. 270:8397-400).

In another embodiment, the transgenic animal is a "knock-in" animal having an alteration in its genome that results in altered expression (e.g., increased (including ectopic) or decreased expression) of the MAPCAX gene, e.g., by introduction of additional copies of MAPCAX, or by operatively inserting a regulatory sequence that provides for altered expression of an endogenous copy of the MAPCAX gene. Such regulatory sequences include inducible, tissue-specific, and constitutive promoters and enhancer elements. The knock-in can be homozygous or heterozygous.

Transgenic nonhuman animals can also be produced that contain selected systems allowing for regulated expression of the transgene. One example of such a system that may be produced is the cre/loxP recombinase system of bacteriophage P1 (Lakso *et al.*, PNAS (1992) 89:6232-6236; U.S. Pat. No. 4,959,317). If a cre/loxP recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the Cre recombinase and a selected protein are required. Such animals can be

provided through the construction of "double" transgenic animals, e.g., by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase. Another example of a recombinase system is the FLP recombinase system of Saccharomyces cerevisiae (O'Gorman et al. (1991) Science 251:1351-1355; U.S. Pat. No. 5,654,182). In a preferred embodiment, both Cre-LoxP and Flp-Frt are used in the same system to regulate expression of the transgene, and for sequential deletion of vector sequences in the same cell (Sun X et al (2000) Nat Genet 25:83-6).

The genetically modified animals can be used in genetic studies to further elucidate the APC and axin pathways, as animal models of disease and disorders implicating defective APC and axin function, and for *in vivo* testing of candidate therapeutic agents, such as those identified in screens described below. The candidate therapeutic agents are administered to a genetically modified animal having altered MAPCAX function and phenotypic changes are compared with appropriate control animals such as genetically modified animals that receive placebo treatment, and/or animals with unaltered MAPCAX expression that receive candidate therapeutic agent.

In addition to the above-described genetically modified animals having altered MAPCAX function, animal models having defective APC and axin function (and otherwise normal MAPCAX function), can be used in the methods of the present invention. For example, a APC and axin knockout mouse can be used to assess, *in vivo*, the activity of a candidate APC and axin modulating agent identified in one of the *in vitro* assays described below. Preferably, the candidate APC and axin modulating agent when administered to a model system with cells defective in APC and axin function, produces a detectable phenotypic change in the model system indicating that the APC and axin function is restored, i.e., the cells exhibit normal cell cycle progression.

Modulating Agents

The invention provides methods to identify agents that interact with and/or modulate the function of MAPCAX and/or the APC and axin pathways. Modulating agents identified by the methods are also part of the invention. Such agents are useful in a variety of diagnostic and therapeutic applications associated with the APC and axin pathways, as well as in further analysis of the MAPCAX protein and its contribution to the APC and axin pathways. Accordingly, the invention also provides methods for

modulating the APC and axin pathways comprising the step of specifically modulating MAPCAX activity by administering a MAPCAX-interacting or -modulating agent.

As used herein, an "MAPCAX-modulating agent" is any agent that modulates MAPCAX function, for example, an agent that interacts with MAPCAX to inhibit or enhance MAPCAX activity or otherwise affect normal MAPCAX function. MAPCAX function can be affected at any level, including transcription, protein expression, protein localization, and cellular or extra-cellular activity. In a preferred embodiment, the MAPCAX - modulating agent specifically modulates the function of the MAPCAX. The phrases "specific modulating agent", "specifically modulates", etc., are used herein to refer to modulating agents that directly bind to the MAPCAX polypeptide or nucleic acid, and preferably inhibit, enhance, or otherwise alter, the function of the MAPCAX. These phrases also encompass modulating agents that alter the interaction of the MAPCAX with a binding partner, substrate, or cofactor (e.g. by binding to a binding partner of a MAPCAX, or to a protein/binding partner complex, and altering MAPCAX function). In a further preferred embodiment, the MAPCAX- modulating agent is a modulator of the APC and axin pathways (e.g. it restores and/or upregulates APC and axin function) and thus is also an APC and axin-modulating agent.

Preferred MAPCAX-modulating agents include small molecule compounds; MAPCAX-interacting proteins, including antibodies and other biotherapeutics; and nucleic acid modulators such as antisense and RNA inhibitors. The modulating agents may be formulated in pharmaceutical compositions, for example, as compositions that may comprise other active ingredients, as in combination therapy, and/or suitable carriers or excipients. Techniques for formulation and administration of the compounds may be found in "Remington's Pharmaceutical Sciences" Mack Publishing Co., Easton, PA, 19th edition.

Small molecule modulators

Small molecules are often preferred to modulate function of proteins with enzymatic function, and/or containing protein interaction domains. Chemical agents, referred to in the art as "small molecule" compounds are typically organic, non-peptide molecules, having a molecular weight up to 10,000, preferably up to 5,000, more preferably up to 1,000, and most preferably up to 500 daltons. This class of modulators includes chemically synthesized molecules, for instance, compounds from combinatorial chemical libraries. Synthetic compounds may be rationally designed or identified based

on known or inferred properties of the MAPCAX protein or may be identified by screening compound libraries. Alternative appropriate modulators of this class are natural products, particularly secondary metabolites from organisms such as plants or fungi, which can also be identified by screening compound libraries for MAPCAX–modulating activity. Methods for generating and obtaining compounds are well known in the art (Schreiber SL, Science (2000) 151: 1964-1969; Radmann J and Gunther J, Science (2000) 151:1947-1948).

Small molecule modulators identified from screening assays, as described below, can be used as lead compounds from which candidate clinical compounds may be designed, optimized, and synthesized. Such clinical compounds may have utility in treating pathologies associated with the APC and axin pathways. The activity of candidate small molecule modulating agents may be improved several-fold through iterative secondary functional validation, as further described below, structure determination, and candidate modulator modification and testing. Additionally, candidate clinical compounds are generated with specific regard to clinical and pharmacological properties. For example, the reagents may be derivatized and re-screened using *in vitro* and *in vivo* assays to optimize activity and minimize toxicity for pharmaceutical development.

Protein Modulators

Specific MAPCAX-interacting proteins are useful in a variety of diagnostic and therapeutic applications related to the APC and axin pathways and related disorders, as well as in validation assays for other MAPCAX-modulating agents. In a preferred embodiment, MAPCAX-interacting proteins affect normal MAPCAX function, including transcription, protein expression, protein localization, and cellular or extra-cellular activity. In another embodiment, MAPCAX-interacting proteins are useful in detecting and providing information about the function of MAPCAX proteins, as is relevant to APC and axin related disorders, such as cancer (e.g., for diagnostic means).

A MAPCAX-interacting protein may be endogenous, i.e. one that naturally interacts genetically or biochemically with a MAPCAX, such as a member of the MAPCAX pathway that modulates MAPCAX expression, localization, and/or activity. MAPCAX-modulators include dominant negative forms of MAPCAX-interacting proteins and of MAPCAX proteins themselves. Yeast two-hybrid and variant screens offer preferred methods for identifying endogenous MAPCAX-interacting proteins (Finley, R. L. et al. (1996) in DNA Cloning-Expression Systems: A Practical Approach, eds. Glover

D. & Hames B. D (Oxford University Press, Oxford, England), pp. 169-203; Fashema SF et al., Gene (2000) 250:1-14; Drees BL Curr Opin Chem Biol (1999) 3:64-70; Vidal M and Legrain P Nucleic Acids Res (1999) 27:919-29; and U.S. Pat. No. 5,928,868). Mass spectrometry is an alternative preferred method for the elucidation of protein complexes (reviewed in, e.g., Pandley A and Mann M, Nature (2000) 405:837-846; Yates JR 3rd, Trends Genet (2000) 16:5-8).

A MAPCAX-interacting protein may be an exogenous protein, such as a MAPCAX-specific antibody or a T-cell antigen receptor (see, e.g., Harlow and Lane (1988) Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory; Harlow and Lane (1999) Using antibodies: a laboratory manual. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press). MAPCAX antibodies are further discussed below.

In preferred embodiments, a MAPCAX-interacting protein specifically binds a MAPCAX protein. In alternative preferred embodiments, a MAPCAX-modulating agent binds a MAPCAX substrate, binding partner, or cofactor.

Antibodies

In another embodiment, the protein modulator is a MAPCAX specific antibody agonist or antagonist. The antibodies have therapeutic and diagnostic utilities, and can be used in screening assays to identify MAPCAX modulators. The antibodies can also be used in dissecting the portions of the MAPCAX pathway responsible for various cellular responses and in the general processing and maturation of the MAPCAX.

Antibodies that specifically bind MAPCAX polypeptides can be generated using known methods. Preferably the antibody is specific to a mammalian ortholog of MAPCAX polypeptide, and more preferably, to human MAPCAX. Antibodies may be polyclonal, monoclonal (mAbs), humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab').sub.2 fragments, fragments produced by a FAb expression library, anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above. Epitopes of MAPCAX which are particularly antigenic can be selected, for example, by routine screening of MAPCAX polypeptides for antigenicity or by applying a theoretical method for selecting antigenic regions of a protein (Hopp and Wood (1981), Proc. Nati. Acad. Sci. U.S.A. 78:3824-28; Hopp and Wood, (1983) Mol. Immunol. 20:483-89; Sutcliffe et al., (1983) Science 219:660-66) to the amino acid sequence of a MAPCAX. Monoclonal antibodies with affinities of 10^8 M^{-1} preferably 10^9 M^{-1} to 10^{10} M^{-1}, or stronger can be made by standard procedures as described (Harlow and Lane, *supra*;

Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed) Academic Press, New York; and U.S. Pat. Nos. 4,381,292; 4,451,570; and 4,618,577). Antibodies may be generated against crude cell extracts of MAPCAX or substantially purified fragments thereof. If MAPCAX fragments are used, they preferably comprise at least 10, and more preferably, at least 20 contiguous amino acids of a MAPCAX protein. In a particular embodiment, MAPCAX-specific antigens and/or immunogens are coupled to carrier proteins that stimulate the immune response. For example, the subject polypeptides are covalently coupled to the keyhole limpet hemocyanin (KLH) carrier, and the conjugate is emulsified in Freund's complete adjuvant, which enhances the immune response. An appropriate immune system such as a laboratory rabbit or mouse is immunized according to conventional protocols.

The presence of MAPCAX-specific antibodies is assayed by an appropriate assay such as a solid phase enzyme-linked immunosorbant assay (ELISA) using immobilized corresponding MAPCAX polypeptides. Other assays, such as radioimmunoassays or fluorescent assays might also be used.

Chimeric antibodies specific to MAPCAX polypeptides can be made that contain different portions from different animal species. For instance, a human immunoglobulin constant region may be linked to a variable region of a murine mAb, such that the antibody derives its biological activity from the human antibody, and its binding specificity from the murine fragment. Chimeric antibodies are produced by splicing together genes that encode the appropriate regions from each species (Morrison et al., Proc. Natl. Acad. Sci. (1984) 81:6851-6855; Neuberger et al., Nature (1984) 312:604-608; Takeda et al., Nature (1985) 31:452-454). Humanized antibodies, which are a form of chimeric antibodies, can be generated by grafting complementary-determining regions (CDRs) (Carlos, T. M., J. M. Harlan. 1994. Blood 84:2068-2101) of mouse antibodies into a background of human framework regions and constant regions by recombinant DNA technology (Riechmann LM, et al., 1988 Nature 323: 323-327). Humanized antibodies contain ~10% murine sequences and ~90% human sequences, and thus further reduce or eliminate immunogenicity, while retaining the antibody specificities (Co MS, and Queen C. 1991 Nature 351: 501-501; Morrison SL. 1992 Ann. Rev. Immun. 10:239-265). Humanized antibodies and methods of their production are well-known in the art (U.S. Pat. Nos. 5,530,101, 5,585,089, 5,693,762, and 6,180,370).

MAPCAX-specific single chain antibodies which are recombinant, single chain polypeptides formed by linking the heavy and light chain fragments of the Fv regions via

an amino acid bridge, can be produced by methods known in the art (U.S. Pat. No. 4,946,778; Bird, Science (1988) 242:423-426; Huston et al., Proc. Natl. Acad. Sci. USA (1988) 85:5879-5883; and Ward et al., Nature (1989) 334:544-546).

Other suitable techniques for antibody production involve in vitro exposure of lymphocytes to the antigenic polypeptides or alternatively to selection of libraries of antibodies in phage or similar vectors (Huse et al., Science (1989) 246:1275-1281). As used herein, T-cell antigen receptors are included within the scope of antibody modulators (Harlow and Lane, 1988, *supra*).

The polypeptides and antibodies of the present invention may be used with or without modification. Frequently, antibodies will be labeled by joining, either covalently or non-covalently, a substance that provides for a detectable signal, or that is toxic to cells that express the targeted protein (Menard S, et al., Int J. Biol Markers (1989) 4:131-134). A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, fluorescent emitting lanthanide metals, chemiluminescent moieties, bioluminescent moieties, magnetic particles, and the like (U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241). Also, recombinant immunoglobulins may be produced (U.S. Pat. No. 4,816,567). Antibodies to cytoplasmic polypeptides may be delivered and reach their targets by conjugation with membrane-penetrating toxin proteins (U.S. Pat. No. 6,086,900).

When used therapeutically in a patient, the antibodies of the subject invention are typically administered parenterally, when possible at the target site, or intravenously. The therapeutically effective dose and dosage regimen is determined by clinical studies. Typically, the amount of antibody administered is in the range of about 0.1 mg/kg –to about 10 mg/kg of patient weight. For parenteral administration, the antibodies are formulated in a unit dosage injectable form (e.g., solution, suspension, emulsion) in association with a pharmaceutically acceptable vehicle. Such vehicles are inherently nontoxic and non-therapeutic. Examples are water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Nonaqueous vehicles such as fixed oils, ethyl oleate, or liposome carriers may also be used. The vehicle may contain minor amounts of additives, such as buffers and preservatives, which enhance isotonicity and chemical stability or otherwise enhance therapeutic potential. The antibodies' concentrations in such vehicles are typically in the range of about 1 mg/ml to about10 mg/ml.

Immunotherapeutic methods are further described in the literature (US Pat. No. 5,859,206; WO0073469).

Nucleic Acid Modulators

Other preferred MAPCAX-modulating agents comprise nucleic acid molecules, such as antisense oligomers or double stranded RNA (dsRNA), which generally inhibit MAPCAX activity. Preferred nucleic acid modulators interfere with the function of the MAPCAX nucleic acid such as DNA replication, transcription, translocation of the MAPCAX RNA to the site of protein translation, translation of protein from the MAPCAX RNA, splicing of the MAPCAX RNA to yield one or more mRNA species, or catalytic activity which may be engaged in or facilitated by the MAPCAX RNA.

In one embodiment, the antisense oligomer is an oligonucleotide that is sufficiently complementary to a MAPCAX mRNA to bind to and prevent translation, preferably by binding to the 5′ untranslated region. MAPCAX-specific antisense oligonucleotides, preferably range from at least 6 to about 200 nucleotides. In some embodiments the oligonucleotide is preferably at least 10, 15, or 20 nucleotides in length. In other embodiments, the oligonucleotide is preferably less than 50, 40, or 30 nucleotides in length. The oligonucleotide can be DNA or RNA or a chimeric mixture or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone. The oligonucleotide may include other appending groups such as peptides, agents that facilitate transport across the cell membrane, hybridization-triggered cleavage agents, and intercalating agents.

In another embodiment, the antisense oligomer is a phosphothioate morpholino oligomer (PMO). PMOs are assembled from four different morpholino subunits, each of which contain one of four genetic bases (A, C, G, or T) linked to a six-membered morpholine ring. Polymers of these subunits are joined by non-ionic phosphodiamidate intersubunit linkages. Details of how to make and use PMOs and other antisense oligomers are well known in the art (e.g. see WO99/18193; Probst JC, Antisense Oligodeoxynucleotide and Ribozyme Design, Methods. (2000) 22(3):271-281; Summerton J, and Weller D. 1997 Antisense Nucleic Acid Drug Dev. :7:187-95; US Pat. No. 5,235,033; and US Pat No. 5,378,841).

Alternative preferred MAPCAX nucleic acid modulators are double-stranded RNA species mediating RNA interference (RNAi). RNAi is the process of sequence-specific,

post-transcriptional gene silencing in animals and plants, initiated by double-stranded RNA (dsRNA) that is homologous in sequence to the silenced gene. Methods relating to the use of RNAi to silence genes in *C. elegans*, *Drosophila*, plants, and humans are known in the art (Fire A, et al., 1998 Nature 391:806-811; Fire, A. Trends Genet. 15, 358-363 (1999); Sharp, P. A. RNA interference 2001. Genes Dev. 15, 485-490 (2001); Hammond, S. M., et al., Nature Rev. Genet. 2, 110-1119 (2001); Tuschl, T. Chem. Biochem. 2, 239-245 (2001); Hamilton, A. et al., Science 286, 950-952 (1999); Hammond, S. M., et al., Nature 404, 293-296 (2000); Zamore, P. D., et al., Cell 101, 25-33 (2000); Bernstein, E., et al., Nature 409, 363-366 (2001); Elbashir, S. M., et al., Genes Dev. 15, 188-200 (2001); WO0129058; WO9932619; Elbashir SM, et al., 2001 Nature 411:494-498).

Nucleic acid modulators are commonly used as research reagents, diagnostics, and therapeutics. For example, antisense oligonucleotides, which are able to inhibit gene expression with exquisite specificity, are often used to elucidate the function of particular genes (see, for example, U.S. Pat. No. 6,165,790). Nucleic acid modulators are also used, for example, to distinguish between functions of various members of a biological pathway. For example, antisense oligomers have been employed as therapeutic moieties in the treatment of disease states in animals and man and have been demonstrated in numerous clinical trials to be safe and effective (Milligan JF, *et al*, Current Concepts in Antisense Drug Design, J Med Chem. (1993) 36:1923-1937; Tonkinson JL *et al.*, Antisense Oligodeoxynucleotides as Clinical Therapeutic Agents, Cancer Invest. (1996) 14:54-65). Accordingly, in one aspect of the invention, a MAPCAX-specific nucleic acid modulator is used in an assay to further elucidate the role of the MAPCAX in the APC and axin pathways, and/or its relationship to other members of the pathway. In another aspect of the invention, a MAPCAX-specific antisense oligomer is used as a therapeutic agent for treatment of APC and axin-related disease states.

Assay Systems

The invention provides assay systems and screening methods for identifying specific modulators of MAPCAX activity. As used herein, an "assay system" encompasses all the components required for performing and analyzing results of an assay that detects and/or measures a particular event. In general, primary assays are used to identify or confirm a modulator's specific biochemical or molecular effect with respect to the MAPCAX nucleic acid or protein. In general, secondary assays further assess the activity of a MAPCAX modulating agent identified by a primary assay and may confirm

that the modulating agent affects MAPCAX in a manner relevant to the APC and axin pathways. In some cases, MAPCAX modulators will be directly tested in a secondary assay.

In a preferred embodiment, the screening method comprises contacting a suitable assay system comprising a MAPCAX polypeptide or nucleic acid with a candidate agent under conditions whereby, but for the presence of the agent, the system provides a reference activity (e.g. binding activity), which is based on the particular molecular event the screening method detects. A statistically significant difference between the agent-biased activity and the reference activity indicates that the candidate agent modulates MAPCAX activity, and hence the APC and axin pathways. The MAPCAX polypeptide or nucleic acid used in the assay may comprise any of the nucleic acids or polypeptides described above.

Primary Assays

The type of modulator tested generally determines the type of primary assay.

Primary assays for small molecule modulators

For small molecule modulators, screening assays are used to identify candidate modulators. Screening assays may be cell-based or may use a cell-free system that recreates or retains the relevant biochemical reaction of the target protein (reviewed in Sittampalam GS *et al.*, Curr Opin Chem Biol (1997) 1:384-91 and accompanying references). As used herein the term "cell-based" refers to assays using live cells, dead cells, or a particular cellular fraction, such as a membrane, endoplasmic reticulum, or mitochondrial fraction. The term "cell free" encompasses assays using substantially purified protein (either endogenous or recombinantly produced), partially purified or crude cellular extracts. Screening assays may detect a variety of molecular events, including protein-DNA interactions, protein-protein interactions (*e.g.*, receptor-ligand binding), transcriptional activity (*e.g.*, using a reporter gene), enzymatic activity (*e.g.*, via a property of the substrate), activity of second messengers, immunogenicty and changes in cellular morphology or other cellular characteristics. Appropriate screening assays may use a wide range of detection methods including fluorescent, radioactive, colorimetric, spectrophotometric, and amperometric methods, to provide a read-out for the particular molecular event detected.

Cell-based screening assays usually require systems for recombinant expression of MAPCAX and any auxiliary proteins demanded by the particular assay. Appropriate methods for generating recombinant proteins produce sufficient quantities of proteins that retain their relevant biological activities and are of sufficient purity to optimize activity and assure assay reproducibility. Yeast two-hybrid and variant screens, and mass spectrometry provide preferred methods for determining protein-protein interactions and elucidation of protein complexes. In certain applications, when MAPCAX-interacting proteins are used in screens to identify small molecule modulators, the binding specificity of the interacting protein to the MAPCAX protein may be assayed by various known methods such as substrate processing (e.g. ability of the candidate MAPCAX-specific binding agents to function as negative effectors in MAPCAX-expressing cells), binding equilibrium constants (usually at least about $10^7 M^{-1}$, preferably at least about $10^8 M^{-1}$, more preferably at least about $10^9 M^{-1}$), and immunogenicity (e.g. ability to elicit MAPCAX specific antibody in a heterologous host such as a mouse, rat, goat or rabbit). For enzymes and receptors, binding may be assayed by, respectively, substrate and ligand processing.

The screening assay may measure a candidate agent's ability to specifically bind to or modulate activity of a MAPCAX polypeptide, a fusion protein thereof, or to cells or membranes bearing the polypeptide or fusion protein. The MAPCAX polypeptide can be full length or a fragment thereof that retains functional MAPCAX activity. The MAPCAX polypeptide may be fused to another polypeptide, such as a peptide tag for detection or anchoring, or to another tag. The MAPCAX polypeptide is preferably human MAPCAX, or is an ortholog or derivative thereof as described above. In a preferred embodiment, the screening assay detects candidate agent-based modulation of MAPCAX interaction with a binding target, such as an endogenous or exogenous protein or other substrate that has MAPCAX –specific binding activity, and can be used to assess normal MAPCAX gene function.

Suitable assay formats that may be adapted to screen for MAPCAX modulators are known in the art. Preferred screening assays are high throughput or ultra high throughput and thus provide automated, cost-effective means of screening compound libraries for lead compounds (Fernandes PB, Curr Opin Chem Biol (1998) 2:597-603; Sundberg SA, Curr Opin Biotechnol 2000, 11:47-53). In one preferred embodiment, screening assays uses fluorescence technologies, including fluorescence polarization, time-resolved fluorescence, and fluorescence resonance energy transfer. These systems offer means to

monitor protein-protein or DNA-protein interactions in which the intensity of the signal emitted from dye-labeled molecules depends upon their interactions with partner molecules (*e.g.*, Selvin PR, Nat Struct Biol (2000) 7:730-4; Fernandes PB, *supra*; Hertzberg RP and Pope AJ, Curr Opin Chem Biol (2000) 4:445-451).

A variety of suitable assay systems may be used to identify candidate MAPCAX and APC and axin pathways modulators (e.g. U.S. Pat. Nos. 5,550,019 and 6,133,437 (apoptosis assays); U.S. Pat. No. 6,114,132 (phosphatase and protease assays), U.S. Pat. Nos. 5,976,782, 6,225,118 and 6,444,434 (angiogenesis assays), among others). Specific preferred assays are described in more detail below.

Protein phosophatases catalyze the removal of a gamma phosphate from a serine, threonine or tyrosine residue in a protein substrate. Since phosphatases act in opposition to kinases, appropriate assays measure the same parameters as kinase assays. In one example, the dephosphorylation of a fluorescently labeled peptide substrate allows trypsin cleavage of the substrate, which in turn renders the cleaved substrate significantly more fluorescent (Nishikata M *et al.*, Biochem J (1999) 343:35-391). In another example, fluorescence polarization (FP), a solution-based, homogeneous technique requiring no immobilization or separation of reaction components, is used to develop high throughput screening (HTS) assays for protein phosphatases. This assay uses direct binding of the phosphatase with the target, and increasing concentrations of target- phosphatase increase the rate of dephosphorylation, leading to a change in polarization (Parker GJ et al., (2000) J Biomol Screen 5:77-88).

Glycosyltransferases mediate changes in glycosylation patterns that, in turn, may affect the function of glycoproteins and/or glycolipids and, further downstream, processes of development, differentiation, transformation and cell-cell recognition. An assay for glycosyltransferase uses scintillation methods to measure the transfer of carbohydrate from radiolabeled sugar-nuecleotide donor to a synthetic glycopolymer acceptor that is coupled to polyacrylamide and coated on plastic microtiter plates (Donovan RS et al., Glycoconj J (1999) 16:607-615).

Assays for ATPase activity are well-known in the art, such as described in Blackburn et al (Blackburn CL, et al., (1999) J Org Chem 64:5565-5570). The ATPase assay is performed using the EnzCheck ATPase kit (Molecular Probes). The assays are performed using an Ultraspec spectrophotometer (Pharmacia), and the progress of the reaction are monitored by absorbance increase at 360 nm. Microtubules (1.7 mM final), kinesin (0.11 mM final), inhibitor (or DMSO blank at 5% final), and the EnzCheck

components (purine nucleotide phosphorylase and MESG substrate) are premixed in the cuvette in a reaction buffer (40 mM PIPES pH 6.8, 5 mM paclitaxel, 1 mM EGTA, 5 mM MgCl2). The reaction is initiated by addition of MgATP (1 mM final).

Apoptosis assays. Assays for apoptosis may be performed by terminal deoxynucleotidyl transferase-mediated digoxigenin-11-dUTP nick end labeling (TUNEL) assay. The TUNEL assay is used to measure nuclear DNA fragmentation characteristic of apoptosis (Lazebnik *et al.*, 1994, Nature 371, 346), by following the incorporation of fluorescein-dUTP (Yonehara *et al.*, 1989, J. Exp. Med. 169, 1747). Apoptosis may further be assayed by acridine orange staining of tissue culture cells (Lucas, R., et al., 1998, Blood 15:4730-41). Other cell-based apoptosis assays include the caspase-3/7 assay and the cell death nucleosome ELISA assay. The caspase 3/7 assay is based on the activation of the caspase cleavage activity as part of a cascade of events that occur during programmed cell death in many apoptotic pathways. In the caspase 3/7 assay (commercially available Apo-ONE™ Homogeneous Caspase-3/7 assay from Promega, cat# 67790), lysis buffer and caspase substrate are mixed and added to cells. The caspase substrate becomes fluorescent when cleaved by active caspase 3/7. The nucleosome ELISA assay is a general cell death assay known to those skilled in the art, and available commercially (Roche, Cat# 1774425). This assay is a quantitative sandwich-enzyme-immunoassay which uses monoclonal antibodies directed against DNA and histones respectively, thus specifically determining amount of mono- and oligonucleosomes in the cytoplasmic fraction of cell lysates. Mono and oligonucleosomes are enriched in the cytoplasm during apoptosis due to the fact that DNA fragmentation occurs several hours before the plasma membrane breaks down, allowing for accumalation in the cytoplasm. Nucleosomes are not present in the cytoplasmic fraction of cells that are not undergoing apoptosis. An apoptosis assay system may comprise a cell that expresses a MAPCAX, and that optionally has defective APC and axin function (e.g. APC and axin is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the apoptosis assay system and changes in induction of apoptosis relative to controls where no test agent is added, identify candidate APC and axin modulating agents. In some embodiments of the invention, an apoptosis assay may be used as a secondary assay to test a candidate APC and axin modulating agents that is initially identified using a cell-free assay system. An apoptosis assay may also be used to test whether MAPCAX function plays a direct role in apoptosis. For example, an apoptosis assay may be performed on cells that over- or under-express

MAPCAX relative to wild type cells. Differences in apoptotic response compared to wild type cells suggests that the MAPCAX plays a direct role in the apoptotic response. Apoptosis assays are described further in US Pat. No. 6,133,437.

Cell proliferation and cell cycle assays. Cell proliferation may be assayed via bromodeoxyuridine (BRDU) incorporation. This assay identifies a cell population undergoing DNA synthesis by incorporation of BRDU into newly-synthesized DNA. Newly-synthesized DNA may then be detected using an anti-BRDU antibody (Hoshino *et al.*, 1986, Int. J. Cancer 38, 369; Campana *et al.*, 1988, J. Immunol. Meth. 107, 79), or by other means.

Cell proliferation is also assayed via phospho-histone H3 staining, which identifies a cell population undergoing mitosis by phosphorylation of histone H3. Phosphorylation of histone H3 at serine 10 is detected using an antibody specfic to the phosphorylated form of the serine 10 residue of histone H3. (Chadlee,D.N. 1995, J. Biol. Chem 270:20098-105). Cell Proliferation may also be examined using [^{3}H]-thymidine incorporation (Chen, J., 1996, Oncogene 13:1395-403; Jeoung, J., 1995, J. Biol. Chem. 270:18367-73). This assay allows for quantitative characterization of S-phase DNA syntheses. In this assay, cells synthesizing DNA will incorporate [^{3}H]-thymidine into newly synthesized DNA. Incorporation can then be measured by standard techniques such as by counting of radioisotope in a scintillation counter (e.g., Beckman LS 3800 Liquid Scintillation Counter). Another proliferation assay uses the dye Alamar Blue (available from Biosource International), which fluoresces when reduced in living cells and provides an indirect measurement of cell number (Voytik-Harbin SL et al., 1998, In Vitro Cell Dev Biol Anim 34:239-46). Yet another proliferation assay, the MTS assay, is based on in vitro cytotoxicity assessment of industrial chemicals, and uses the soluble tetrazolium salt, MTS. MTS assays are commercially available, for example, the Promega CellTiter 96® AQueous Non-Radioactive Cell Proliferation Assay (Cat.# G5421).

Cell proliferation may also be assayed by colony formation in soft agar (Sambrook et al., Molecular Cloning, Cold Spring Harbor (1989)). For example, cells transformed with MAPCAX are seeded in soft agar plates, and colonies are measured and counted after two weeks incubation.

Cell proliferation may also be assayed by measuring ATP levels as indicator of metabolically active cells. Such assays are commercially available, for example Cell Titer-Glo™, which is a luminescent homogeneous assay available from Promega.

Involvement of a gene in the cell cycle may be assayed by flow cytometry (Gray JW et al. (1986) Int J Radiat Biol Relat Stud Phys Chem Med 49:237-55). Cells transfected with a MAPCAX may be stained with propidium iodide and evaluated in a flow cytometer (available from Becton Dickinson), which indicates accumulation of cells in different stages of the cell cycle.

Accordingly, a cell proliferation or cell cycle assay system may comprise a cell that expresses a MAPCAX, and that optionally has defective APC and axin function (e.g. APC and axin is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the assay system and changes in cell proliferation or cell cycle relative to controls where no test agent is added, identify candidate APC and axin modulating agents. In some embodiments of the invention, the cell proliferation or cell cycle assay may be used as a secondary assay to test a candidate APC and axin modulating agents that is initially identified using another assay system such as a cell-free assay system. A cell proliferation assay may also be used to test whether MAPCAX function plays a direct role in cell proliferation or cell cycle. For example, a cell proliferation or cell cycle assay may be performed on cells that over- or under-express MAPCAX relative to wild type cells. Differences in proliferation or cell cycle compared to wild type cells suggests that the MAPCAX plays a direct role in cell proliferation or cell cycle.

Angiogenesis. Angiogenesis may be assayed using various human endothelial cell systems, such as umbilical vein, coronary artery, or dermal cells. Suitable assays include Alamar Blue based assays (available from Biosource International) to measure proliferation; migration assays using fluorescent molecules, such as the use of Becton Dickinson Falcon HTS FluoroBlock cell culture inserts to measure migration of cells through membranes in presence or absence of angiogenesis enhancer or suppressors; and tubule formation assays based on the formation of tubular structures by endothelial cells on Matrigel® (Becton Dickinson). Accordingly, an angiogenesis assay system may comprise a cell that expresses a MAPCAX, and that optionally has defective APC and axin function (e.g. APC and axin is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the angiogenesis assay system and changes in angiogenesis relative to controls where no test agent is added, identify candidate APC and axin modulating agents. In some embodiments of the invention, the angiogenesis assay may be used as a secondary assay to test a candidate APC and axin modulating agents that is initially identified using another assay system. An angiogenesis assay may also be used

to test whether MAPCAX function plays a direct role in cell proliferation. For example, an angiogenesis assay may be performed on cells that over- or under-express MAPCAX relative to wild type cells. Differences in angiogenesis compared to wild type cells suggests that the MAPCAX plays a direct role in angiogenesis. U.S. Pat. Nos. 5,976,782, 6,225,118 and 6,444,434, among others, describe various angiogenesis assays.

Hypoxic induction. The alpha subunit of the transcription factor, hypoxia inducible factor-1 (HIF-1), is upregulated in tumor cells following exposure to hypoxia in vitro. Under hypoxic conditions, HIF-1 stimulates the expression of genes known to be important in tumour cell survival, such as those encoding glyolytic enzymes and VEGF. Induction of such genes by hypoxic conditions may be assayed by growing cells transfected with MAPCAX in hypoxic conditions (such as with 0.1% O2, 5% CO2, and balance N2, generated in a Napco 7001 incubator (Precision Scientific)) and normoxic conditions, followed by assessment of gene activity or expression by Taqman®. For example, a hypoxic induction assay system may comprise a cell that expresses a MAPCAX, and that optionally has defective APC and axin function (e.g. APC and axin is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the hypoxic induction assay system and changes in hypoxic response relative to controls where no test agent is added, identify candidate APC and axin modulating agents. In some embodiments of the invention, the hypoxic induction assay may be used as a secondary assay to test a candidate APC and axin modulating agents that is initially identified using another assay system. A hypoxic induction assay may also be used to test whether MAPCAX function plays a direct role in the hypoxic response. For example, a hypoxic induction assay may be performed on cells that over- or under-express MAPCAX relative to wild type cells. Differences in hypoxic response compared to wild type cells suggests that the MAPCAX plays a direct role in hypoxic induction.

Cell adhesion. Cell adhesion assays measure adhesion of cells to purified adhesion proteins, or adhesion of cells to each other, in presence or absence of candidate modulating agents. Cell-protein adhesion assays measure the ability of agents to modulate the adhesion of cells to purified proteins. For example, recombinant proteins are produced, diluted to 2.5g/mL in PBS, and used to coat the wells of a microtiter plate. The wells used for negative control are not coated. Coated wells are then washed, blocked with 1% BSA, and washed again. Compounds are diluted to 2x final test concentration

and added to the blocked, coated wells. Cells are then added to the wells, and the unbound cells are washed off. Retained cells are labeled directly on the plate by adding a membrane-permeable fluorescent dye, such as calcein-AM, and the signal is quantified in a fluorescent microplate reader.

Cell-cell adhesion assays measure the ability of agents to modulate binding of cell adhesion proteins with their native ligands. These assays use cells that naturally or recombinantly express the adhesion protein of choice. In an exemplary assay, cells expressing the cell adhesion protein are plated in wells of a multiwell plate. Cells expressing the ligand are labeled with a membrane-permeable fluorescent dye, such as BCECF , and allowed to adhere to the monolayers in the presence of candidate agents. Unbound cells are washed off, and bound cells are detected using a fluorescence plate reader.

High-throughput cell adhesion assays have also been described. In one such assay, small molecule ligands and peptides are bound to the surface of microscope slides using a microarray spotter, intact cells are then contacted with the slides, and unbound cells are washed off. In this assay, not only the binding specificity of the peptides and modulators against cell lines are determined, but also the functional cell signaling of attached cells using immunofluorescence techniques in situ on the microchip is measured (Falsey JR et al., Bioconjug Chem. 2001 May-Jun;12(3):346-53).

Tubulogenesis. Tubulogenesis assays monitor the ability of cultured cells, generally endothelial cells, to form tubular structures on a matrix substrate, which generally simulates the environment of the extracellular matrix. Exemplary substrates include Matrigel™ (Becton Dickinson), an extract of basement membrane proteins containing laminin, collagen IV, and heparin sulfate proteoglycan, which is liquid at 4° C and forms a solid gel at 37° C. Other suitable matrices comprise extracellular components such as collagen, fibronectin, and/or fibrin. Cells are stimulated with a pro-angiogenic stimulant, and their ability to form tubules is detected by imaging. Tubules can generally be detected after an overnight incubation with stimuli, but longer or shorter time frames may also be used. Tube formation assays are well known in the art (e.g., Jones MK et al., 1999, Nature Medicine 5:1418-1423). These assays have traditionally involved stimulation with serum or with the growth factors FGF or VEGF. Serum represents an undefined source of growth factors. In a preferred embodiment, the assay is performed with cells cultured in serum free medium, in order to control which process or pathway a

candidate agent modulates. Moreover, we have found that different target genes respond differently to stimulation with different pro-angiogenic agents, including inflammatory angiogenic factors such as TNF-alpa. Thus, in a further preferred embodiment, a tubulogenesis assay system comprises testing a MAPCAX's response to a variety of factors, such as FGF, VEGF, phorbol myristate acetate (PMA), TNF-alpha, ephrin, etc.

Cell Migration. An invasion/migration assay (also called a migration assay) tests the ability of cells to overcome a physical barrier and to migrate towards pro-angiogenic signals. Migration assays are known in the art (e.g., Paik JH et al., 2001, J Biol Chem 276:11830-11837). In a typical experimental set-up, cultured endothelial cells are seeded onto a matrix-coated porous lamina, with pore sizes generally smaller than typical cell size. The matrix generally simulates the environment of the extracellular matrix, as described above. The lamina is typically a membrane, such as the transwell polycarbonate membrane (Corning Costar Corporation, Cambridge, MA), and is generally part of an upper chamber that is in fluid contact with a lower chamber containing pro-angiogenic stimuli. Migration is generally assayed after an overnight incubation with stimuli, but longer or shorter time frames may also be used. Migration is assessed as the number of cells that crossed the lamina, and may be detected by staining cells with hemotoxylin solution (VWR Scientific, South San Francisco, CA), or by any other method for determining cell number. In another exemplary set up, cells are fluorescently labeled and migration is detected using fluorescent readings, for instance using the Falcon HTS FluoroBlok (Becton Dickinson). While some migration is observed in the absence of stimulus, migration is greatly increased in response to pro-angiogenic factors. As described above, a preferred assay system for migration/invasion assays comprises testing a MAPCAX's response to a variety of pro-angiogenic factors, including tumor angiogenic and inflammatory angiogenic agents, and culturing the cells in serum free medium.

Sprouting assay. A sprouting assay is a three-dimensional *in vitro* angiogenesis assay that uses a cell-number defined spheroid aggregation of endothelial cells ("spheroid"), embedded in a collagen gel-based matrix. The spheroid can serve as a starting point for the sprouting of capillary-like structures by invasion into the extracellular matrix (termed "cell sprouting") and the subsequent formation of complex anastomosing networks (Korff and Augustin, 1999, J Cell Sci 112:3249-58). In an exemplary experimental set-up, spheroids are prepared by pipetting 400 human umbilical

vein endothelial cells into individual wells of a nonadhesive 96-well plates to allow overnight spheroidal aggregation (Korff and Augustin: J Cell Biol 143: 1341-52, 1998). Spheroids are harvested and seeded in 900μl of methocel-collagen solution and pipetted into individual wells of a 24 well plate to allow collagen gel polymerization. Test agents are added after 30 min by pipetting 100 μl of 10-fold concentrated working dilution of the test substances on top of the gel. Plates are incubated at 37°C for 24h. Dishes are fixed at the end of the experimental incubation period by addition of paraformaldehyde. Sprouting intensity of endothelial cells can be quantitated by an automated image analysis system to determine the cumulative sprout length per spheroid.

Primary assays for antibody modulators

For antibody modulators, appropriate primary assays test is a binding assay that tests the antibody's affinity to and specificity for the MAPCAX protein. Methods for testing antibody affinity and specificity are well known in the art (Harlow and Lane, 1988, 1999, *supra*). The enzyme-linked immunosorbant assay (ELISA) is a preferred method for detecting MAPCAX-specific antibodies; others include FACS assays, radioimmunoassays, and fluorescent assays.

In some cases, screening assays described for small molecule modulators may also be used to test antibody modulators.

Primary assays for nucleic acid modulators

For nucleic acid modulators, primary assays may test the ability of the nucleic acid modulator to inhibit or enhance MAPCAX gene expression, preferably mRNA expression. In general, expression analysis comprises comparing MAPCAX expression in like populations of cells (*e.g.*, two pools of cells that endogenously or recombinantly express MAPCAX) in the presence and absence of the nucleic acid modulator. Methods for analyzing mRNA and protein expression are well known in the art. For instance, Northern blotting, slot blotting, ribonuclease protection, quantitative RT-PCR (*e.g.*, using the TaqMan®, PE Applied Biosystems), or microarray analysis may be used to confirm that MAPCAX mRNA expression is reduced in cells treated with the nucleic acid modulator (*e.g.*, Current Protocols in Molecular Biology (1994) Ausubel FM *et al.*, *eds.*, John Wiley & Sons, Inc., chapter 4; Freeman WM *et al.*, Biotechniques (1999) 26:112-125; Kallioniemi OP, Ann Med 2001, 33:142-147; Blohm DH and Guiseppi-Elie, A Curr Opin Biotechnol 2001, 12:41-47). Protein expression may also be monitored. Proteins are most

commonly detected with specific antibodies or antisera directed against either the MAPCAX protein or specific peptides. A variety of means including Western blotting, ELISA, or in situ detection, are available (Harlow E and Lane D, 1988 and 1999, *supra*).

In some cases, screening assays described for small molecule modulators, particularly in assay systems that involve MAPCAX mRNA expression, may also be used to test nucleic acid modulators.

Secondary Assays

Secondary assays may be used to further assess the activity of MAPCAX-modulating agent identified by any of the above methods to confirm that the modulating agent affects MAPCAX in a manner relevant to the APC and axin pathways. As used herein, MAPCAX-modulating agents encompass candidate clinical compounds or other agents derived from previously identified modulating agent. Secondary assays can also be used to test the activity of a modulating agent on a particular genetic or biochemical pathway or to test the specificity of the modulating agent's interaction with MAPCAX.

Secondary assays generally compare like populations of cells or animals (*e.g.*, two pools of cells or animals that endogenously or recombinantly express MAPCAX) in the presence and absence of the candidate modulator. In general, such assays test whether treatment of cells or animals with a candidate MAPCAX–modulating agent results in changes in the APC and axin pathways in comparison to untreated (or mock- or placebo-treated) cells or animals. Certain assays use "sensitized genetic backgrounds", which, as used herein, describe cells or animals engineered for altered expression of genes in the APC and axin or interacting pathways.

Cell-based assays

Cell based assays may detect endogenous APC and axin pathways activity or may rely on recombinant expression of APC and axin pathways components. Any of the aforementioned assays may be used in this cell-based format. Candidate modulators are typically added to the cell media but may also be injected into cells or delivered by any other efficacious means.

Animal Assays

A variety of non-human animal models of normal or defective APC and axin pathways may be used to test candidate MAPCAX modulators. Models for defective APC

and axin pathways typically use genetically modified animals that have been engineered to mis-express (*e.g.*, over-express or lack expression in) genes involved in the APC and axin pathways. Assays generally require systemic delivery of the candidate modulators, such as by oral administration, injection, etc.

In a preferred embodiment, APC and axin pathways activity is assessed by monitoring neovascularization and angiogenesis. Animal models with defective and normal APC and axin are used to test the candidate modulator's affect on MAPCAX in Matrigel® assays. Matrigel® is an extract of basement membrane proteins, and is composed primarily of laminin, collagen IV, and heparin sulfate proteoglycan. It is provided as a sterile liquid at 4° C, but rapidly forms a solid gel at 37° C. Liquid Matrigel® is mixed with various angiogenic agents, such as bFGF and VEGF, or with human tumor cells which over-express the MAPCAX. The mixture is then injected subcutaneously(SC) into female athymic nude mice (Taconic, Germantown, NY) to support an intense vascular response. Mice with Matrigel® pellets may be dosed via oral (PO), intraperitoneal (IP), or intravenous (IV) routes with the candidate modulator. Mice are euthanized 5 - 12 days post-injection, and the Matrigel® pellet is harvested for hemoglobin analysis (Sigma plasma hemoglobin kit). Hemoglobin content of the gel is found to correlate the degree of neovascularization in the gel.

In another preferred embodiment, the effect of the candidate modulator on MAPCAX is assessed via tumorigenicity assays. Tumor xenograft assays are known in the art (see, e.g., Ogawa K et al., 2000, Oncogene 19:6043-6052). Xenografts are typically implanted SC into female athymic mice, 6-7 week old, as single cell suspensions either from a pre-existing tumor or from *in vitro* culture. The tumors which express the MAPCAX endogenously are injected in the flank, 1 x 10^5 to 1 x 10^7 cells per mouse in a volume of 100 μL using a 27gauge needle. Mice are then ear tagged and tumors are measured twice weekly. Candidate modulator treatment is initiated on the day the mean tumor weight reaches 100 mg. Candidate modulator is delivered IV, SC, IP, or PO by bolus administration. Depending upon the pharmacokinetics of each unique candidate modulator, dosing can be performed multiple times per day. The tumor weight is assessed by measuring perpendicular diameters with a caliper and calculated by multiplying the measurements of diameters in two dimensions. At the end of the experiment, the excised tumors maybe utilized for biomarker identification or further analyses. For immunohistochemistry staining, xenograft tumors are fixed in 4% paraformaldehyde,

0.1M phosphate, pH 7.2, for 6 hours at 4°C, immersed in 30% sucrose in PBS, and rapidly frozen in isopentane cooled with liquid nitrogen.

In another preferred embodiment, tumorogenicity is monitored using a hollow fiber assay, which is described in U.S. Pat No. US 5,698,413. Briefly, the method comprises implanting into a laboratory animal a biocompatible, semi-permeable encapsulation device containing target cells, treating the laboratory animal with a candidate modulating agent, and evaluating the target cells for reaction to the candidate modulator. Implanted cells are generally human cells from a pre-existing tumor or a tumor cell line. After an appropriate period of time, generally around six days, the implanted samples are harvested for evaluation of the candidate modulator. Tumorogenicity and modulator efficacy may be evaluated by assaying the quantity of viable cells present in the macrocapsule, which can be determined by tests known in the art, for example, MTT dye conversion assay, neutral red dye uptake, trypan blue staining, viable cell counts, the number of colonies formed in soft agar, the capacity of the cells to recover and replicate in vitro, etc.

In another preferred embodiment, a tumorogenicity assay use a transgenic animal, usually a mouse, carrying a dominant oncogene or tumor suppressor gene knockout under the control of tissue specific regulatory sequences; these assays are generally referred to as transgenic tumor assays. In a preferred application, tumor development in the transgenic model is well characterized or is controlled. In an exemplary model, the "RIP1-Tag2" transgene, comprising the SV40 large T-antigen oncogene under control of the insulin gene regulatory regions is expressed in pancreatic beta cells and results in islet cell carcinomas (Hanahan D, 1985, Nature 315:115-122; Parangi S et al, 1996, Proc Natl Acad Sci USA 93: 2002-2007; Bergers G et al, 1999, Science 284:808-812). An "angiogenic switch," occurs at approximately five weeks, as normally quiescent capillaries in a subset of hyperproliferative islets become angiogenic. The RIP1-TAG2 mice die by age 14 weeks. Candidate modulators may be administered at a variety of stages, including just prior to the angiogenic switch (e.g., for a model of tumor prevention), during the growth of small tumors (e.g., for a model of intervention), or during the growth of large and/or invasive tumors (e.g., for a model of regression). Tumorogenicity and modulator efficacy can be evaluating life-span extension and/or tumor characteristics, including number of tumors, tumor size, tumor morphology, vessel density, apoptotic index, etc.

Diagnostic and therapeutic uses

Specific MAPCAX-modulating agents are useful in a variety of diagnostic and therapeutic applications where disease or disease prognosis is related to defects in the APC and axin pathways, such as angiogenic, apoptotic, or cell proliferation disorders. Accordingly, the invention also provides methods for modulating the APC and axin pathways in a cell, preferably a cell pre-determined to have defective or impaired APC and axin function (e.g. due to overexpression, underexpression, or misexpression of APC and axin, or due to gene mutations), comprising the step of administering an agent to the cell that specifically modulates MAPCAX activity. Preferably, the modulating agent produces a detectable phenotypic change in the cell indicating that the APC and axin function is restored. The phrase "function is restored", and equivalents, as used herein, means that the desired phenotype is achieved, or is brought closer to normal compared to untreated cells. For example, with restored APC and axin function, cell proliferation and/or progression through cell cycle may normalize, or be brought closer to normal relative to untreated cells. The invention also provides methods for treating disorders or disease associated with impaired APC and axin function by administering a therapeutically effective amount of a MAPCAX -modulating agent that modulates the APC and axin pathways. The invention further provides methods for modulating MAPCAX function in a cell, preferably a cell pre-determined to have defective or impaired MAPCAX function, by administering a MAPCAX -modulating agent. Additionally, the invention provides a method for treating disorders or disease associated with impaired MAPCAX function by administering a therapeutically effective amount of a MAPCAX -modulating agent.

The discovery that MAPCAX is implicated in APC and axin pathways provides for a variety of methods that can be employed for the diagnostic and prognostic evaluation of diseases and disorders involving defects in the APC and axin pathways and for the identification of subjects having a predisposition to such diseases and disorders.

Various expression analysis methods can be used to diagnose whether MAPCAX expression occurs in a particular sample, including Northern blotting, slot blotting, ribonuclease protection, quantitative RT-PCR, and microarray analysis. (*e.g.*, Current Protocols in Molecular Biology (1994) Ausubel FM *et al., eds.*, John Wiley & Sons, Inc., chapter 4; Freeman WM *et al.*, Biotechniques (1999) 26:112-125; Kallioniemi OP, Ann Med 2001, 33:142-147; Blohm and Guiseppi-Elie, Curr Opin Biotechnol 2001, 12:41-47). Tissues having a disease or disorder implicating defective APC and axin signaling that express a MAPCAX, are identified as amenable to treatment with a MAPCAX modulating

agent. In a preferred application, the APC and axin defective tissue overexpresses a MAPCAX relative to normal tissue. For example, a Northern blot analysis of mRNA from tumor and normal cell lines, or from tumor and matching normal tissue samples from the same patient, using full or partial MAPCAX cDNA sequences as probes, can determine whether particular tumors express or overexpress MAPCAX. Alternatively, the TaqMan® is used for quantitative RT-PCR analysis of MAPCAX expression in cell lines, normal tissues and tumor samples (PE Applied Biosystems).

Various other diagnostic methods may be performed, for example, utilizing reagents such as the MAPCAX oligonucleotides, and antibodies directed against a MAPCAX, as described above for: (1) the detection of the presence of MAPCAX gene mutations, or the detection of either over- or under-expression of MAPCAX mRNA relative to the non-disorder state; (2) the detection of either an over- or an under-abundance of MAPCAX gene product relative to the non-disorder state; and (3) the detection of perturbations or abnormalities in the signal transduction pathway mediated by MAPCAX.

Thus, in a specific embodiment, the invention is drawn to a method for diagnosing a disease or disorder in a patient that is associated with alterations in MAPCAX expression, the method comprising: a) obtaining a biological sample from the patient; b) contacting the sample with a probe for MAPCAX expression; c) comparing results from step (b) with a control; and d) determining whether step (c) indicates a likelihood of the disease or disorder. Preferably, the disease is cancer. The probe may be either DNA or protein, including an antibody.

EXAMPLES

The following experimental section and examples are offered by way of illustration and not by way of limitation.

I. C. elegans Axin/APC Suppressor Screen

We have discovered that while RNAi of *apr-1* in a wildtype background does not produce a Muv phenotype, *apr-1* inactivation enhances the penetrance of the Muv phenotype of the *pry-1* mutant to 95% (see also Gleason et al., *supra*). This enhancement of the *pry-1* Muv phenotype requires wildtype *bar-1*/beta-catenin and *pop-1*/TCF activity, suggesting that *apr-1* normally negatively regulates beta-catenin. beta-catenin-specific suppressor genes, when inactivated, likely suppress beta-catenin's inappropriate

transcriptional activation of target genes and, therefore, may be relevant for cancer therapy.

We designed a genetic screen to identify genes in addition to *bar-1*/beta-catenin and *pop-1*/TCF that act positively in beta-catenin signaling and, when inactivated, suppress the Muv mutant phenotype of *pry-1 (mu38); apr-1 (RNAi)*. The function of individual genes was inactivated by RNAi in *pry-1* mutant L1 larvae, in combination with *apr-1* RNAi, and suppression of the Muv phenotype was scored as a statistically significant increase in the proportion of adults that did not display the Muv phenotype. Suppressor genes were subsequently counterscreened to eliminate those that appeared to suppress the *pry-1 (mu38); apr-1 (RNAi)* mutant non-specifically, rather than those that specifically function in beta-catenin signaling. Suppressor genes that passed two specificity assays were considered to be beta-catenin-specific suppressors. First, these suppressors, like *bar-1*/beta-catenin, do not suppress the Muv phenotype of three mutations in genes unrelated to beta-catenin signaling (*let-60*/Ras, *lin-12*/Notch, and *lin-15*). Second, these suppressors are not generally defective in the RNAi response, as determined by co-RNAi with genes unrelated to beta-catenin signaling.

II. <u>Analysis of Table 1</u>

BLAST analysis (Altschul et al., *supra*) was employed to identify orthologs of *C. elegans* modifiers. The columns "MAPCAX symbol", and "MAPCAX name aliases " provide a symbol and the known name abbreviations for the Targets, where available, from Genbank. "MAPCAX RefSeq_NA or GI_NA", "MAPCAX GI_AA", "MAPCAX NAME", and "MAPCAX Description" provide the reference DNA sequences for the MAPCAXs as available from National Center for Biology Information (NCBI), MAPCAX protein Genbank identifier number (GI#), MAPCAX name, and MAPCAX description, all available from Genbank, respectively. The length of each amino acid is in the "MAPCAX Protein Length" column.

Names and Protein sequences of *C. elegans* modifiers of APC and axin from screen (Example I), are represented in the "Modifier Name" and "Modifier GI_AA" column by GI#, respectively.

Table1

MAPCAX symbol	MAPCAX name aliases	MAPCAX RefSeq_NA or GI_NA	NA SEQ ID NO:	MAPCAX GI_AA or RefSeq_AA	AA SEQ ID NO:	MAPCAX name	MAPCAX description	MAPCAX protein length	Modifier name	Modifier GI_AA
LOC256129	LOC256129 | similar to UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 1; beta-1,3-N-acetylglucosaminyltransferase; beta-1,3-N-acetylglucosaminyltransferase 1; UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase, polypeptide 6 | na	XM_171955.1	1	22051164	27	similar to UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 1; beta-1,3-N-acetylglucosaminyltransferase; beta-1,3-N-acetylglucosaminyltransferase 1; UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase, polypeptide 6	na	397	T15D6.5	17509057
MGC4655	MGC4655 | hypothetical protein MGC4655	NM_033309.1	2	15208631	28	hypothetical protein MGC4655	transferase; transferase; UDP-galactose beta-N-acetylglucosamine beta-1,3-galactosyltransferase	377	T15D6.5	17509057
B3GNT4	B3GNT4 | B3GN-T4 | beta3Gn-T4 | beta-1,3-N-acetylglucosaminyltransferase bGn-T4 | UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 4	NM_030765.1|XM_039199.1	3	13540527	29	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 4	transferase, transferring glycosyl groups; acetylglucosaminyltransferase	378	T15D6.5	17509057

B3GNT3	B3GNT3 | TMEM3 | B3GN-T3 | B3GNT-3 | HP10328 | B3GAL-T8 | beta3Gn-T3 | transmembrane protein 3 | putative type II membrane protein | beta-1,3-N-acetylglucosaminyltransferase bGnT-3 | UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 3	NM_014256.2	4	7657172	30	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 3	acetylglucosaminyltransferase	372	T15D6.5	17509057
B3GNT7	B3GNT7 | hypothetical gene supported by AK000770 | UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 7	NM_145236.1|XM_048735.1	5	21687139	31	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 7	transferase; UDP-galactose beta-N-acetylglucosamine beta-1,3-galactosyltransferase	401	T15D6.5	17509057
B3GNT1	B3GNT1 | B3GNT | B3GN-T1 | B3GN-T2 | B3GNT-2 | BETA3GNT | beta3gal-T5 gene | beta-1,3-N-acetylglucosaminyltransferase bGnT-1 | beta-1,3-N-acetylglucosaminyltransferase bGnT-2 | UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 1	NM_006577.3|NM_033252.1	6	9845238	32	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 1	acetylglucosaminyltransferase; N-acetyllactosamine synthase	397	T15D6.5	17509057
IMAGE:4907098	IMAGE:4907098 | B3Gn-T6 | beta-1,3-N-acetylglucosaminyltransferase protein	NM_138706.1|XM_166247.1	7	20162576	33	beta-1,3-N-acetylglucosaminyltransferase protein	acetylglucosaminyltransferase	384	T15D6.5	17509057

CHL1	CHL1 | CALL | L1CAM2 | cell adhesion molecule with homology to L1CAM (close homologue of L1) | cell adhesion molecule with homology to L1CAM (close homolog of L1)	NM_006614.1	8	5729767	34	cell adhesion molecule with homology to L1CAM (close homolog of L1)	cell adhesion molecule	1224	lad-1	17538700
L1CAM	L1CAM | HSAS | MASA | MIC5 | SPG1 | CAML1 | CD171 | HSAS1 | N-CAML1 | L1 cell adhesion molecule | neural cell adhesion molecule L1 | L1 cell adhesion molecule (hydrocephalus, stenosis of aqueduct of Sylvius 1, MASA (mental retardation, aphasia, shuffling gait and adducted thumbs) syndrome, spastic paraplegia 1)	NM_000425.2|NM_024003.1	9	13435353	35	L1 cell adhesion molecule (hydrocephalus, stenosis of aqueduct of Sylvius 1, MASA (mental retardation, aphasia, shuffling gait and adducted thumbs) syndrome, spastic paraplegia 1)	cell adhesion molecule; cell adhesion molecule; cell adhesion molecule; cytoskeletal protein binding; integrin binding	1253	lad-1	17538700
NFASC	NFASC | KIAA0756 | neurofascin	XM_046808.8	10	27478636	36	neurofascin	cell adhesion molecule; cell adhesion molecule; protein binding; cytoskeletal protein binding; transmembrane receptor	1066	lad-1	17538700

HUS1	HUS1 | HUS1 (S. pombe) checkpoint homolog | HUS1 checkpoint homolog (S. pombe)	NM_004507.1	11	4758576	37	HUS1 checkpoint homolog (S. pombe)	DNA binding; protein binding; ATP binding; DNA clamp loader	280	hus-1	17507989
HUS1b	HUS1b | similar to HUS1 checkpoint homolog (S. pombe); HUS1 (S. pombe) checkpoint homolog	NM_148959.1	12	22507374	38	similar to HUS1 checkpoint homolog (S. pombe); HUS1 (S. pombe) checkpoint homolog	protein binding	278	hus-1	17507989
FLJ12735	FLJ12735 | hypothetical protein FLJ12735	NM_024857.3	13	26080431	39	hypothetical protein FLJ12735	ATP binding; DNA clamp loader	1844	rfc-1	17563226
RFC1	RFC1 | A1 | RFC | PO-GA | RECC1 | MHCBFB | RFC140 | replication factor C1 | MHC binding factor, beta | replication factor C (activator 1) 1 (145kD) | replication factor C (activator 1) 1, 145kDa	NM_002913.2|NM_006081	14	15011931	40	replication factor C (activator 1) 1, 145kDa	DNA dependent adenosinetriphosphatase; enzyme activator; enzyme activator; ATP binding; DNA clamp loader	1148	rfc-1	17563226
PPP4C	PPP4C | PP4 | PPX | Protein phosphatase 4, catalytic subunit | protein phosphatase 4 (formerly X), catalytic subunit	NM_002720	15	4506027	41	protein phosphatase 4 (formerly X), catalytic subunit	protein serine/threonine phosphatase; protein phosphatase; protein phosphatase	307	pph-4.2	17554398
YME1L1	YME1L1 | FTSH | MEG4 | YME1L | ATP-dependent metalloprotease FtsH1 homolog | YME1-like 1 (S. cerevisiae)	NM_014263|NM_139312|NM_139313	16	21327685	42	YME1-like 1 (S. cerevisiae)	ATPase; ATPase; ATP binding; ATP binding; metallopeptidase; metallopeptidase; chaperone; peptidase; zinc binding	773	3L509	17554264

EHD1	EHD1 | PAST | HPAST | H-PAST | testilin | EH domain containing 1 | homolog of Drosophila past | EH-domain containing 1	NM_006795	17	5803009	43	EH-domain containing 1	protein binding; insulin-like growth factor receptor binding	534	rme-1	17565130
EHD2	EHD2 | EH domain containing 2 | EH-domain containing 2	NM_014601	18	21361462	44	EH-domain containing 2	nucleotide binding; protein binding	543	rme-1	17565130
EHD3	EHD3 | EH domain containing 3 | EH-domain containing 3	NM_014600	19	7657056	45	EH-domain containing 3	nucleotide binding	535	rme-1	17565130
EHD4	EHD4 | EH domain containing 4 | ortholog of rat pincher | EH-domain containing 4	NM_139265	20	21264315	46	EH-domain containing 4	collagen binding; nucleotide binding; calcium ion binding	541	rme-1	17565130
KIAA0963	KIAA0963 | FLJ00173 | KIAA0963 protein	NM_014963	21	7662410	47	KIAA0963 protein	na	1366	nsh-1	17553078
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NRCAM	NRCAM | KIAA0343 | Bravo | neuronal cell adhesion molecule	NM_005010.1	53	4826864	54	neuronal cell adhesion molecule	cell adhesion molecule	1180	Lad-1	17538700

III. High-Throughput In Vitro Fluorescence Polarization Assay

Fluorescently-labeled MAPCAX peptide/substrate are added to each well of a 96-well microtiter plate, along with a test agent in a test buffer (10 mM HEPES, 10 mM NaCl, 6 mM magnesium chloride, pH 7.6). Changes in fluorescence polarization, determined by using a Fluorolite FPM-2 Fluorescence Polarization Microtiter System (Dynatech Laboratories, Inc), relative to control values indicates the test compound is a candidate modifier of MAPCAX activity.

IV. High-Throughput In Vitro Binding Assay.

^{33}P-labeled MAPCAX peptide is added in an assay buffer (100 mM KCl, 20 mM HEPES pH 7.6, 1 mM $MgCl_2$, 1% glycerol, 0.5% NP-40, 50 mM beta-mercaptoethanol, 1 mg/ml BSA, cocktail of protease inhibitors) along with a test agent to the wells of a Neutralite-avidin coated assay plate and incubated at 25°C for 1 hour. Biotinylated substrate is then added to each well and incubated for 1 hour. Reactions are stopped by washing with PBS, and counted in a scintillation counter. Test agents that cause a difference in activity relative to control without test agent are identified as candidate APC and axin modulating agents.

V. Immunoprecipitations and Immunoblotting

For coprecipitation of transfected proteins, 3×10^6 appropriate recombinant cells containing the MAPCAX proteins are plated on 10-cm dishes and transfected on the following day with expression constructs. The total amount of DNA is kept constant in each transfection by adding empty vector. After 24 h, cells are collected, washed once with phosphate-buffered saline and lysed for 20 min on ice in 1 ml of lysis buffer

containing 50 mM Hepes, pH 7.9, 250 mM NaCl, 20 mM -glycerophosphate, 1 mM sodium orthovanadate, 5 mM p-nitrophenyl phosphate, 2 mM dithiothreitol, protease inhibitors (complete, Roche Molecular Biochemicals), and 1% Nonidet P-40. Cellular debris is removed by centrifugation twice at 15,000 × g for 15 min. The cell lysate is incubated with 25 μl of M2 beads (Sigma) for 2 h at 4 °C with gentle rocking.

After extensive washing with lysis buffer, proteins bound to the beads are solubilized by boiling in SDS sample buffer, fractionated by SDS-polyacrylamide gel electrophoresis, transferred to polyvinylidene difluoride membrane and blotted with the indicated antibodies. The reactive bands are visualized with horseradish peroxidase coupled to the appropriate secondary antibodies and the enhanced chemiluminescence (ECL) Western blotting detection system (Amersham Pharmacia Biotech).

VI. Expression analysis

All cell lines used in the following experiments are NCI (National Cancer Institute) lines, and are available from ATCC (American Type Culture Collection, Manassas, VA 20110-2209). Normal and tumor tissues are obtained from Impath, UC Davis, Clontech, Stratagene, Ardais, Genome Collaborative, and Ambion.

TaqMan® analysis is used to assess expression levels of the disclosed genes in various samples.

RNA is extracted from each tissue sample using Qiagen (Valencia, CA) RNeasy kits, following manufacturer's protocols, to a final concentration of 50ng/μl. Single stranded cDNA is then synthesized by reverse transcribing the RNA samples using random hexamers and 500ng of total RNA per reaction, following protocol 4304965 of Applied Biosystems (Foster City, CA).

Primers for expression analysis using TaqMan® assay (Applied Biosystems, Foster City, CA) are prepared according to the TaqMan® protocols, and the following criteria: a) primer pairs are designed to span introns to eliminate genomic contamination, and b) each primer pair produced only one product. Expression analysis is performed using a 7900HT instrument.

TaqMan® reactions are carried out following manufacturer's protocols, in 25 μl total volume for 96-well plates and 10 μl total volume for 384-well plates, using 300nM primer and 250 nM probe, and approximately 25ng of cDNA. The standard curve for result analysis is prepared using a universal pool of human cDNA samples, which is a mixture of cDNAs from a wide variety of tissues so that the chance that a target will be

present in appreciable amounts is good. The raw data are normalized using 18S rRNA (universally expressed in all tissues and cells).

For each expression analysis, tumor tissue samples are compared with matched normal tissues from the same patient. A gene is considered overexpressed in a tumor when the level of expression of the gene is 2 fold or higher in the tumor compared with its matched normal sample. In cases where normal tissue is not available, a universal pool of cDNA samples is used instead. In these cases, a gene is considered overexpressed in a tumor sample when the difference of expression levels between a tumor sample and the average of all normal samples from the same tissue type is greater than 2 times the standard deviation of all normal samples (i.e., Tumor – average(all normal samples) > 2 x STDEV(all normal samples)).

A modulator identified by an assay described herein can be further validated for therapeutic effect by administration to a tumor in which the gene is overexpressed. A decrease in tumor growth confirms therapeutic utility of the modulator. Prior to treating a patient with the modulator, the likelihood that the patient will respond to treatment can be diagnosed by obtaining a tumor sample from the patient, and assaying for expression of the gene targeted by the modulator. The expression data for the gene(s) can also be used as a diagnostic marker for disease progression. The assay can be performed by expression analysis as described above, by antibody directed to the gene target, or by any other available detection method.

WHAT IS CLAIMED IS:

1. A method of identifying a candidate APC and axin pathways modulating agent, said method comprising the steps of:

(a) providing an assay system comprising a MAPCAX polypeptide or nucleic acid;

(b) contacting the assay system with a test agent under conditions whereby, but for the presence of the test agent, the system provides a reference activity; and

(c) detecting a test agent-biased activity of the assay system, wherein a difference between the test agent-biased activity and the reference activity identifies the test agent as a candidate APC and axin pathways modulating agent.

2. The method of Claim 1 wherein the assay system comprises cultured cells that express the MAPCAX polypeptide.

3. The method of Claim 2 wherein the cultured cells additionally have defective APC and axin function.

4. The method of Claim 1 wherein the assay system includes a screening assay comprising a MAPCAX polypeptide, and the candidate test agent is a small molecule modulator.

5. The method of Claim 4 wherein the assay is a binding assay.

6. The method of Claim 1 wherein the assay system is selected from the group consisting of an apoptosis assay system, a cell proliferation assay system, an angiogenesis assay system, and a hypoxic induction assay system.

7. The method of Claim 1 wherein the assay system includes a binding assay comprising a MAPCAX polypeptide and the candidate test agent is an antibody.

8. The method of Claim 1 wherein the assay system includes an expression assay comprising a MAPCAX nucleic acid and the candidate test agent is a nucleic acid modulator.

9. The method of Claim 8 wherein the nucleic acid modulator is an antisense oligomer.

10. The method of Claim 8 wherein the nucleic acid modulator is a PMO.

11. The method of Claim 1 additionally comprising:

(d) administering the candidate APC and axin pathways modulating agent identified in (c) to a model system comprising cells defective in APC and axin function and, detecting a phenotypic change in the model system that indicates that the APC and axin function is restored.

12. The method of Claim 11 wherein the model system is a mouse model with defective APC and axin function.

13. A method for modulating a APC and axin pathways of a cell comprising contacting a cell defective in APC and axin function with a candidate modulator that specifically binds to a MAPCAX polypeptide, whereby APC and axin function is restored.

14. The method of Claim 13 wherein the candidate modulator is administered to a vertebrate animal predetermined to have a disease or disorder resulting from a defect in APC and axin function.

15. The method of Claim 13 wherein the candidate modulator is selected from the group consisting of an antibody and a small molecule.

16. The method of Claim 1, comprising the additional steps of:

(e) providing a secondary assay system comprising cultured cells or a non-human animal expressing MAPCAX ,

(f) contacting the secondary assay system with the test agent of (b) or an agent derived therefrom under conditions whereby, but for the presence of the test agent or agent derived therefrom, the system provides a reference activity; and

(g) detecting an agent-biased activity of the second assay system,

wherein a difference between the agent-biased activity and the reference activity of the second assay system confirms the test agent or agent derived therefrom as a candidate APC and axin pathways modulating agent,

and wherein the second assay detects an agent-biased change in the APC and axin pathways.

17. The method of Claim 16 wherein the secondary assay system comprises cultured cells.

18. The method of Claim 16 wherein the secondary assay system comprises a non-human animal.

19. The method of Claim 18 wherein the non-human animal mis-expresses a APC and axin pathways gene.

20. A method of modulating APC and axin pathways in a mammalian cell comprising contacting the cell with an agent that specifically binds a MAPCAX polypeptide or nucleic acid.

21. The method of Claim 20 wherein the agent is administered to a mammalian animal predetermined to have a pathology associated with the APC and axin pathways.

22. The method of Claim 20 wherein the agent is a small molecule modulator, a nucleic acid modulator, or an antibody.

23. A method for diagnosing a disease in a patient comprising:

(a) obtaining a biological sample from the patient;

(b) contacting the sample with a probe for MAPCAX expression;

(c) comparing results from step (b) with a control;

(d) determining whether step (c) indicates a likelihood of disease.

24. The method of Claim 23 wherein said disease is cancer.

SEQUENCE LISTING

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gctcaataaa tataaactaa tgag 5544

<210> 27
<211> 397
<212> PRT
<213> Homo sapiens

<400> 27

Met Arg Cys Pro Lys Cys Leu Leu Cys Leu Ser Ala Leu Leu Thr Leu
1 5 10 15

Leu Gly Leu Lys Val Tyr Ile Glu Trp Thr Ser Glu Ser Arg Leu Ser
20 25 30

Lys Ala Tyr Pro Ser Pro Arg Gly Thr Pro Pro Ser Pro Thr Pro Ala
35 40 45

Asn Pro Glu Pro Thr Leu Pro Ala Asn Leu Ser Thr Arg Leu Gly Gln
50 55 60

Thr Ile Pro Leu Pro Phe Ala Tyr Trp Asn Gln Gln Gln Trp Arg Leu
65 70 75 80

Gly Ser Leu Pro Ser Gly Asp Ser Thr Glu Thr Gly Gly Cys Gln Ala
85 90 95

Trp Gly Ala Ala Ala Ala Thr Glu Ile Pro Asp Phe Ala Ser Tyr Pro
100 105 110

Lys Asp Leu Arg Arg Phe Leu Leu Ser Ala Ala Cys Arg Ser Phe Pro
115 120 125

Gln Trp Leu Pro Gly Gly Gly Gly Ser Gln Val Ser Ser Cys Ser Asp
    130   135   140

Thr Asp Val Pro Tyr Leu Leu Leu Ala Val Lys Ser Glu Pro Gly Arg
145   150   155   160

Phe Ala Glu Arg Gln Ala Val Arg Glu Thr Trp Gly Ser Pro Ala Pro
                165   170   175

Gly Ile Arg Leu Leu Phe Leu Leu Gly Ser Pro Val Gly Glu Ala Gly
            180   185   190

Pro Asp Leu Asp Ser Leu Val Ala Trp Glu Ser Arg Arg Tyr Ser Asp
        195   200   205

Leu Leu Leu Trp Asp Phe Leu Asp Val Pro Phe Asn Gln Thr Leu Lys
    210   215   220

Asp Leu Leu Leu Leu Ala Trp Leu Gly Arg His Cys Pro Thr Val Ser
225   230   235   240

Phe Val Leu Arg Ala Gln Asp Asp Ala Phe Val His Thr Pro Ala Leu
                245   250   255

Leu Ala His Leu Arg Ala Leu Pro Pro Ala Ser Ala Arg Ser Leu Tyr
            260   265   270

Leu Gly Glu Val Phe Thr Gln Ala Met Pro Leu Arg Lys Pro Gly Gly
        275   280   285

Pro Phe Tyr Val Pro Glu Ser Phe Phe Glu Gly Gly Tyr Pro Ala Tyr
    290   295   300

Ala Ser Gly Gly Gly Tyr Val Ile Ala Gly Arg Leu Ala Pro Trp Leu
305   310   315   320

Leu Arg Ala Ala Ala Arg Val Ala Pro Phe Pro Phe Glu Asp Val Tyr
                325   330   335

Thr Gly Leu Cys Ile Arg Ala Leu Gly Leu Val Pro Gln Ala His Pro
            340   345   350

Gly Phe Leu Thr Ala Trp Pro Ala Asp Arg Thr Ala Asp His Cys Ala
        355   360   365

Phe Arg Asn Leu Leu Leu Val Arg Pro Leu Gly Pro Gln Ala Ser Ile

370 375 380

Arg Leu Trp Lys Gln Leu Gln Asp Pro Arg Leu Gln Cys
385 390 395

<210> 28
<211> 377
<212> PRT
<213> Homo sapiens

<400> 28

Met Arg Ser Ala Thr Ala Arg Pro Arg Arg Arg Ala Arg Arg Glu Gly
1 5 10 15

Glu Gly Gly Arg His Arg Gly Pro Pro Pro Asp Pro Ala Arg Ser Ser
20 25 30

Tyr Pro Thr Arg Val Gln Pro Arg Arg Pro Thr Lys Gly Thr His Arg
35 40 45

Arg Arg Pro Arg Leu Arg Asp Pro Phe Asp Phe Ala Arg Tyr Leu Arg
50 55 60

Ala Lys Asp Gln Arg Arg Phe Pro Leu Leu Ile Asn Gln Pro His Lys
65 70 75 80

Cys Arg Gly Asp Gly Ala Pro Gly Gly Arg Pro Asp Leu Leu Ile Ala
85 90 95

Val Lys Ser Val Ala Glu Asp Phe Glu Arg Arg Gln Ala Val Arg Gln
100 105 110

Thr Trp Gly Ala Glu Gly Arg Val Gln Gly Ala Leu Val Arg Arg Val
115 120 125

Phe Leu Leu Gly Val Pro Arg Gly Ala Gly Ser Gly Gly Ala Asp Glu
130 135 140

Val Gly Glu Gly Ala Arg Thr His Trp Arg Ala Leu Leu Arg Ala Glu
145 150 155 160

Ser Leu Ala Tyr Ala Asp Ile Leu Leu Trp Ala Phe Asp Asp Thr Phe
165 170 175

Phe Asn Leu Thr Leu Lys Glu Ile His Phe Leu Ala Trp Ala Ser Ala
180 185 190

Phe Cys Pro Asp Val Arg Phe Val Phe Lys Gly Asp Ala Asp Val Phe
195 200 205

Val Asn Val Gly Asn Leu Leu Glu Phe Leu Ala Pro Arg Asp Pro Ala
210 215 220

Gln Asp Leu Leu Ala Gly Asp Val Ile Val His Ala Arg Pro Ile Arg
225 230 235 240

Thr Arg Ala Ser Lys Tyr Tyr Ile Pro Glu Ala Val Tyr Gly Leu Pro
245 250 255

Ala Tyr Pro Ala Tyr Ala Gly Gly Gly Gly Phe Val Leu Ser Gly Ala
260 265 270

Thr Leu His Arg Leu Ala Gly Ala Cys Ala Gln Val Glu Leu Phe Pro
275 280 285

Ile Asp Asp Val Phe Leu Gly Met Cys Leu Gln Arg Leu Arg Leu Thr
290 295 300

Pro Glu Pro His Pro Ala Phe Arg Thr Phe Gly Ile Pro Gln Pro Ser
305 310 315 320

Ala Ala Pro His Leu Ser Thr Phe Asp Pro Cys Phe Tyr Arg Glu Leu
325 330 335

Val Val Val His Gly Leu Ser Ala Ala Asp Ile Trp Leu Met Trp Arg
340 345 350

Leu Leu His Gly Pro His Gly Pro Ala Cys Ala His Pro Gln Pro Val
355 360 365

Ala Ala Gly Pro Phe Gln Trp Asp Ser
370 375

<210> 29
<211> 378
<212> PRT
<213> Homo sapiens

<400> 29

Met Leu Pro Pro Gln Pro Ser Ala Ala His Gln Gly Arg Gly Gly Arg
1 5 10 15

Ser Gly Leu Leu Pro Lys Gly Pro Ala Met Leu Cys Arg Leu Cys Trp
20 25 30

Leu Val Ser Tyr Ser Leu Ala Val Leu Leu Leu Gly Cys Leu Leu Phe
35 40 45

Leu Arg Lys Ala Ala Lys Pro Ala Gly Asp Pro Thr Ala His Gln Pro
50 55 60

Phe Trp Ala Pro Pro Thr Pro Arg His Ser Arg Cys Pro Pro Asn His
65 70 75 80

Thr Val Ser Ser Ala Ser Leu Ser Leu Pro Ser Arg His Arg Leu Phe
85 90 95

Leu Thr Tyr Arg His Cys Arg Asn Phe Ser Ile Leu Leu Glu Pro Ser
100 105 110

Gly Cys Ser Lys Asp Thr Phe Leu Leu Leu Ala Ile Lys Ser Gln Pro
115 120 125

Gly His Val Glu Arg Arg Ala Ala Ile Arg Ser Thr Trp Gly Arg Val
130 135 140

Gly Gly Trp Ala Arg Gly Arg Gln Leu Lys Leu Val Phe Leu Leu Gly
145 150 155 160

Val Ala Gly Ser Ala Pro Pro Ala Gln Leu Leu Ala Tyr Glu Ser Arg
165 170 175

Glu Phe Asp Asp Ile Leu Gln Trp Asp Phe Thr Glu Asp Phe Phe Asn
180 185 190

Leu Thr Leu Lys Glu Leu His Leu Gln Arg Trp Val Val Ala Ala Cys
195 200 205

Pro Gln Ala His Phe Met Leu Lys Gly Asp Asp Asp Val Phe Val His
210 215 220

Val Pro Asn Val Leu Glu Phe Leu Asp Gly Trp Asp Pro Ala Gln Asp
225 230 235 240

Leu Leu Val Gly Asp Val Ile Arg Gln Ala Leu Pro Asn Arg Asn Thr
245 250 255

Lys Val Lys Tyr Phe Ile Pro Pro Ser Met Tyr Arg Ala Thr His Tyr
260 265 270

Pro Pro Tyr Ala Gly Gly Gly Gly Tyr Val Met Ser Arg Ala Thr Val

275 280 285

Arg Arg Leu Gln Ala Ile Met Glu Asp Ala Glu Leu Phe Pro Ile Asp
290 295 300

Asp Val Phe Val Gly Met Cys Leu Arg Arg Leu Gly Leu Ser Pro Met
305 310 315 320

His His Ala Gly Phe Lys Thr Phe Gly Ile Arg Arg Pro Leu Asp Pro
325 330 335

Leu Asp Pro Cys Leu Tyr Arg Gly Leu Leu Leu Val His Arg Leu Ser
340 345 350

Pro Leu Glu Met Trp Thr Met Trp Ala Leu Val Thr Asp Glu Gly Leu
355 360 365

Lys Cys Ala Ala Gly Pro Ile Pro Gln Arg
370 375

<210> 30
<211> 372
<212> PRT
<213> Homo sapiens

<400> 30

Met Lys Tyr Leu Arg His Arg Arg Pro Asn Ala Thr Leu Ile Leu Ala
1 5 10 15

Ile Gly Ala Phe Thr Leu Leu Leu Phe Ser Leu Leu Val Ser Pro Pro
20 25 30

Thr Cys Lys Val Gln Glu Gln Pro Pro Ala Ile Pro Glu Ala Leu Ala
35 40 45

Trp Pro Thr Pro Pro Thr Arg Pro Ala Pro Ala Pro Cys His Ala Asn
50 55 60

Thr Ser Met Val Thr His Pro Asp Phe Ala Thr Gln Pro Gln His Val
65 70 75 80

Gln Asn Phe Leu Leu Tyr Arg His Cys Arg His Phe Pro Leu Leu Gln
85 90 95

Asp Val Pro Pro Ser Lys Cys Ala Gln Pro Val Phe Leu Leu Leu Val
100 105 110

Ile Lys Ser Ser Pro Ser Asn Tyr Val Arg Arg Glu Leu Leu Arg Arg
115 120 125

Thr Trp Gly Arg Glu Arg Lys Val Arg Gly Leu Gln Leu Arg Leu Leu
130 135 140

Phe Leu Val Gly Thr Ala Ser Asn Pro His Glu Ala Arg Lys Val Asn
145 150 155 160

Arg Leu Leu Glu Leu Glu Ala Gln Thr His Gly Asp Ile Leu Gln Trp
165 170 175

Asp Phe His Asp Ser Phe Phe Asn Leu Thr Leu Lys Gln Val Leu Phe
180 185 190

Leu Gln Trp Gln Glu Thr Arg Cys Ala Asn Ala Ser Phe Val Leu Asn
195 200 205

Gly Asp Asp Asp Val Phe Ala His Thr Asp Asn Met Val Phe Tyr Leu
210 215 220

Gln Asp His Asp Pro Gly Arg His Leu Phe Val Gly Gln Leu Ile Gln
225 230 235 240

Asn Val Gly Pro Ile Arg Ala Phe Trp Ser Lys Tyr Tyr Val Pro Glu
245 250 255

Val Val Thr Gln Asn Glu Arg Tyr Pro Pro Tyr Cys Gly Gly Gly Gly
260 265 270

Phe Leu Leu Ser Arg Phe Thr Ala Ala Ala Leu Arg Arg Ala Ala His
275 280 285

Val Leu Asp Ile Phe Pro Ile Asp Asp Val Phe Leu Gly Met Cys Leu
290 295 300

Glu Leu Glu Gly Leu Lys Pro Ala Ser His Ser Gly Ile Arg Thr Ser
305 310 315 320

Gly Val Arg Ala Pro Ser Gln His Leu Ser Ser Phe Asp Pro Cys Phe
325 330 335

Tyr Arg Asp Leu Leu Leu Val His Arg Phe Leu Pro Tyr Glu Met Leu
340 345 350

Leu Met Trp Asp Ala Leu Asn Gln Pro Asn Leu Thr Cys Gly Asn Gln
355 360 365

Thr Gln Ile Tyr
    370

<210> 31
<211> 401
<212> PRT
<213> Homo sapiens

<400> 31

Met Ser Leu Trp Lys Lys Thr Val Tyr Arg Ser Leu Cys Leu Ala Leu
1   5   10   15

Ala Leu Leu Val Ala Val Thr Val Phe Gln Arg Ser Leu Thr Pro Gly
            20   25   30

Gln Phe Leu Gln Glu Pro Pro Pro Pro Thr Leu Glu Pro Gln Lys Ala
        35   40   45

Gln Lys Pro Asn Gly Gln Leu Val Asn Pro Asn Asn Phe Trp Lys Asn
    50   55   60

Pro Lys Asp Val Ala Ala Pro Thr Pro Met Ala Ser Gln Gly Pro Gln
65   70   75   80

Ala Trp Asp Val Thr Thr Thr Asn Cys Ser Ala Asn Ile Asn Leu Thr
                85   90   95

His Gln Pro Trp Phe Gln Val Leu Glu Pro Gln Phe Arg Gln Phe Leu
            100   105   110

Phe Tyr Arg His Cys Arg Tyr Phe Pro Met Leu Leu Asn His Pro Glu
        115   120   125

Lys Cys Arg Gly Asp Val Tyr Leu Leu Val Val Val Lys Ser Val Ile
    130   135   140

Thr Gln His Asp Arg Arg Glu Ala Ile Arg Gln Thr Trp Gly Arg Glu
145   150   155   160

Arg Gln Ser Ala Gly Gly Gly Arg Gly Ala Val Arg Thr Leu Phe Leu
                165   170   175

Leu Gly Thr Ala Ser Lys Gln Glu Glu Arg Thr His Tyr Gln Gln Leu
            180   185   190

Leu Ala Tyr Glu Asp Arg Leu Tyr Gly Asp Ile Leu Gln Trp Gly Phe

195 200 205

Leu Asp Thr Phe Phe Asn Leu Thr Leu Lys Glu Ile His Phe Leu Lys
210 215 220

Trp Leu Asp Ile Tyr Cys Pro His Val Pro Phe Ile Phe Lys Gly Asp
225 230 235 240

Asp Asp Val Phe Val Asn Pro Thr Asn Leu Leu Glu Phe Leu Ala Asp
245 250 255

Arg Gln Pro Gln Glu Asn Leu Phe Val Gly Asp Val Leu Gln His Ala
260 265 270

Arg Pro Ile Arg Arg Lys Asp Asn Lys Tyr Tyr Ile Pro Gly Ala Leu
275 280 285

Tyr Gly Lys Ala Ser Tyr Pro Pro Tyr Ala Gly Gly Gly Gly Phe Leu
290 295 300

Met Ala Gly Ser Leu Ala Arg Arg Leu His His Ala Cys Asp Thr Leu
305 310 315 320

Glu Leu Tyr Pro Ile Asp Asp Val Phe Leu Gly Met Cys Leu Glu Val
325 330 335

Leu Gly Val Gln Pro Thr Ala His Glu Gly Phe Lys Thr Phe Gly Ile
340 345 350

Ser Arg Asn Arg Asn Ser Arg Met Asn Lys Glu Pro Cys Phe Phe Arg
355 360 365

Ala Met Leu Val Val His Lys Leu Leu Pro Pro Glu Leu Leu Ala Met
370 375 380

Trp Gly Leu Val His Ser Asn Leu Thr Cys Ser Arg Lys Leu Gln Val
385 390 395 400

Leu

<210> 32
<211> 397
<212> PRT
<213> Homo sapiens

<400> 32

Met Ser Val Gly Arg Arg Arg Ile Lys Leu Leu Gly Ile Leu Met Met
1 5 10 15

Ala Asn Val Phe Ile Tyr Phe Ile Met Glu Val Ser Lys Ser Ser Ser
20 25 30

Gln Glu Lys Asn Gly Lys Gly Glu Val Ile Ile Pro Lys Glu Lys Phe
35 40 45

Trp Lys Ile Ser Thr Pro Pro Glu Ala Tyr Trp Asn Arg Glu Gln Glu
50 55 60

Lys Leu Asn Arg Gln Tyr Asn Pro Ile Leu Ser Met Leu Thr Asn Gln
65 70 75 80

Thr Gly Glu Ala Gly Arg Leu Ser Asn Ile Ser His Leu Asn Tyr Cys
85 90 95

Glu Pro Asp Leu Arg Val Thr Ser Val Val Thr Gly Phe Asn Asn Leu
100 105 110

Pro Asp Arg Phe Lys Asp Phe Leu Leu Tyr Leu Arg Cys Arg Asn Tyr
115 120 125

Ser Leu Leu Ile Asp Gln Pro Asp Lys Cys Ala Lys Lys Pro Phe Leu
130 135 140

Leu Leu Ala Ile Lys Ser Leu Thr Pro His Phe Ala Arg Arg Gln Ala
145 150 155 160

Ile Arg Glu Ser Trp Gly Gln Glu Ser Asn Ala Gly Asn Gln Thr Val
165 170 175

Val Arg Val Phe Leu Leu Gly Gln Thr Pro Pro Glu Asp Asn His Pro
180 185 190

Asp Leu Ser Asp Met Leu Lys Phe Glu Ser Glu Lys His Gln Asp Ile
195 200 205

Leu Met Trp Asn Tyr Arg Asp Thr Phe Phe Asn Leu Ser Leu Lys Glu
210 215 220

Val Leu Phe Leu Arg Trp Val Ser Thr Ser Cys Pro Asp Thr Glu Phe
225 230 235 240

Val Phe Lys Gly Asp Asp Asp Val Phe Val Asn Thr His His Ile Leu
245 250 255

Asn Tyr Leu Asn Ser Leu Ser Lys Thr Lys Ala Lys Asp Leu Phe Ile
260 265 270

Gly Asp Val Ile His Asn Ala Gly Pro His Arg Asp Lys Lys Leu Lys
275 280 285

Tyr Tyr Ile Pro Glu Val Val Tyr Ser Gly Leu Tyr Pro Pro Tyr Ala
290 295 300

Gly Gly Gly Gly Phe Leu Tyr Ser Gly His Leu Ala Leu Arg Leu Tyr
305 310 315 320

His Ile Thr Asp Gln Val His Leu Tyr Pro Ile Asp Asp Val Tyr Thr
325 330 335

Gly Met Cys Leu Gln Lys Leu Gly Leu Val Pro Glu Lys His Lys Gly
340 345 350

Phe Arg Thr Phe Asp Ile Glu Glu Lys Asn Lys Asn Asn Ile Cys Ser
355 360 365

Tyr Val Asp Leu Met Leu Val His Ser Arg Lys Pro Gln Glu Met Ile
370 375 380

Asp Ile Trp Ser Gln Leu Gln Ser Ala His Leu Lys Cys
385 390 395

<210> 33
<211> 384
<212> PRT
<213> Homo sapiens

<400> 33

Met Ala Phe Pro Cys Arg Arg Ser Leu Thr Ala Lys Thr Leu Ala Cys
1 5 10 15

Leu Leu Val Gly Val Ser Phe Leu Ala Leu Gln Gln Trp Phe Leu Gln
20 25 30

Ala Pro Arg Ser Pro Arg Glu Glu Arg Ser Pro Gln Glu Glu Thr Pro
35 40 45

Glu Gly Pro Thr Asp Ala Pro Ala Ala Asp Glu Pro Pro Ser Glu Leu
50 55 60

Val Pro Gly Pro Pro Cys Val Ala Asn Ala Ser Ala Asn Ala Thr Ala

65 70 75 80

Asp Phe Glu Gln Leu Pro Ala Arg Ile Gln Asp Phe Leu Arg Tyr Arg
85 90 95

His Cys Arg His Phe Pro Leu Leu Trp Asp Ala Pro Ala Lys Cys Ala
100 105 110

Gly Gly Arg Gly Val Phe Leu Leu Leu Ala Val Lys Ser Ala Pro Glu
115 120 125

His Tyr Glu Arg Arg Glu Leu Ile Arg Arg Thr Trp Gly Gln Glu Arg
130 135 140

Ser Tyr Gly Gly Arg Pro Val Arg Arg Leu Phe Leu Leu Gly Thr Pro
145 150 155 160

Gly Pro Glu Asp Glu Ala Arg Ala Glu Arg Leu Ala Glu Leu Val Ala
165 170 175

Leu Glu Ala Arg Glu His Gly Asp Val Leu Gln Trp Ala Phe Ala Asp
180 185 190

Thr Phe Leu Asn Leu Thr Leu Lys His Leu His Leu Leu Asp Trp Leu
195 200 205

Ala Ala Arg Cys Pro His Ala Arg Phe Leu Leu Ser Gly Asp Asp Asp
210 215 220

Val Phe Val His Thr Ala Asn Val Val Arg Phe Leu Gln Ala Gln Pro
225 230 235 240

Pro Gly Arg His Leu Phe Ser Gly Gln Leu Met Glu Gly Ser Val Pro
245 250 255

Ile Arg Asp Ser Trp Ser Lys Tyr Phe Val Pro Pro Gln Leu Phe Pro
260 265 270

Gly Ser Ala Tyr Pro Val Tyr Cys Ser Gly Gly Gly Phe Leu Leu Ser
275 280 285

Gly Pro Thr Ala Arg Ala Leu Arg Ala Ala Ala Arg His Thr Pro Leu
290 295 300

Phe Pro Ile Asp Asp Ala Tyr Met Gly Met Cys Leu Glu Arg Ala Gly
305 310 315 320

Leu Ala Pro Ser Gly His Glu Gly Ile Arg Pro Phe Gly Val Gln Leu
325 330 335

Pro Gly Ala Gln Gln Ser Ser Phe Asp Pro Cys Met Tyr Arg Glu Leu
340 345 350

Leu Leu Val His Arg Phe Ala Pro Tyr Glu Met Leu Leu Met Trp Lys
355 360 365

Ala Leu His Ser Pro Ala Leu Ser Cys Asp Arg Gly His Arg Val Ser
370 375 380

<210> 34
<211> 1224
<212> PRT
<213> Homo sapiens

<400> 34

Met Glu Pro Leu Leu Leu Gly Arg Gly Leu Ile Val Tyr Leu Met Phe
1 5 10 15

Leu Leu Leu Lys Phe Ser Lys Ala Ile Glu Ile Pro Ser Ser Val Gln
20 25 30

Gln Val Pro Thr Ile Ile Lys Gln Ser Lys Val Gln Val Ala Phe Pro
35 40 45

Phe Asp Glu Tyr Phe Gln Ile Glu Cys Glu Ala Lys Gly Asn Pro Glu
50 55 60

Pro Thr Phe Ser Trp Thr Lys Asp Gly Asn Pro Phe Tyr Phe Thr Asp
65 70 75 80

His Arg Ile Ile Pro Ser Asn Asn Ser Gly Thr Phe Arg Ile Pro Asn
85 90 95

Glu Gly His Ile Ser His Phe Gln Gly Lys Tyr Arg Cys Phe Ala Ser
100 105 110

Asn Lys Leu Gly Ile Ala Met Ser Glu Glu Ile Glu Phe Ile Val Pro
115 120 125

Ser Val Pro Lys Phe Pro Lys Glu Lys Ile Asp Pro Leu Glu Val Glu
130 135 140

Glu Gly Asp Pro Ile Val Leu Pro Cys Asn Pro Pro Lys Gly Leu Pro
145 150 155 160

Pro Leu His Ile Tyr Trp Met Asn Ile Glu Leu Glu His Ile Glu Gln
165 170 175

Asp Glu Arg Val Tyr Met Ser Gln Lys Gly Asp Leu Tyr Phe Ala Asn
180 185 190

Val Glu Glu Lys Asp Ser Arg Asn Asp Tyr Cys Cys Phe Ala Ala Phe
195 200 205

Pro Arg Leu Arg Thr Ile Val Gln Lys Met Pro Met Lys Leu Thr Val
210 215 220

Asn Ser Leu Lys His Ala Asn Asp Ser Ser Ser Ser Thr Glu Ile Gly
225 230 235 240

Ser Lys Ala Asn Ser Ile Lys Gln Arg Lys Pro Lys Leu Leu Leu Pro
245 250 255

Pro Thr Glu Ser Gly Ser Glu Ser Ser Ile Thr Ile Leu Lys Gly Glu
260 265 270

Ile Leu Leu Leu Glu Cys Phe Ala Glu Gly Leu Pro Thr Pro Gln Val
275 280 285

Asp Trp Asn Lys Ile Gly Gly Asp Leu Pro Lys Gly Arg Glu Ala Lys
290 295 300

Glu Asn Tyr Gly Lys Thr Leu Lys Ile Glu Asn Val Ser Tyr Gln Asp
305 310 315 320

Lys Gly Asn Tyr Arg Cys Thr Ala Ser Asn Phe Leu Gly Thr Ala Thr
325 330 335

His Asp Phe His Val Ile Val Glu Glu Pro Pro Arg Trp Thr Lys Lys
340 345 350

Pro Gln Ser Ala Val Tyr Ser Thr Gly Ser Asn Gly Ile Leu Leu Cys
355 360 365

Glu Ala Glu Gly Glu Pro Gln Pro Thr Ile Lys Trp Arg Val Asn Gly
370 375 380

Ser Pro Val Asp Asn His Pro Phe Ala Gly Asp Val Val Phe Pro Arg
385 390 395 400

Glu Ile Ser Phe Thr Asn Leu Gln Pro Asn His Thr Ala Val Tyr Gln
405 410 415

Cys Glu Ala Ser Asn Val His Gly Thr Ile Leu Ala Asn Ala Asn Ile
420 425 430

Asp Val Val Asp Val Arg Pro Leu Ile Gln Thr Lys Asp Gly Glu Asn
435 440 445

Tyr Ala Thr Val Val Gly Tyr Ser Ala Phe Leu His Cys Glu Phe Phe
450 455 460

Ala Ser Pro Glu Ala Val Val Ser Trp Gln Lys Val Glu Glu Val Lys
465 470 475 480

Pro Leu Glu Gly Arg Arg Tyr His Ile Tyr Glu Asn Gly Thr Leu Gln
485 490 495

Ile Asn Arg Thr Thr Glu Glu Asp Ala Gly Ser Tyr Ser Cys Trp Val
500 505 510

Glu Asn Ala Ile Gly Lys Thr Ala Val Thr Ala Asn Leu Asp Ile Arg
515 520 525

Asn Ala Thr Lys Leu Arg Val Ser Pro Lys Asn Pro Arg Ile Pro Lys
530 535 540

Leu His Met Leu Glu Leu His Cys Glu Ser Lys Cys Asp Ser His Leu
545 550 555 560

Lys His Ser Leu Lys Leu Ser Trp Ser Lys Asp Gly Glu Ala Phe Glu
565 570 575

Ile Asn Gly Thr Glu Asp Gly Arg Ile Ile Ile Asp Gly Ala Asn Leu
580 585 590

Thr Ile Ser Asn Val Thr Leu Glu Asp Gln Gly Ile Tyr Cys Cys Ser
595 600 605

Ala His Thr Ala Leu Asp Ser Ala Ala Asp Ile Thr Gln Val Thr Val
610 615 620

Leu Asp Val Pro Asp Pro Pro Glu Asn Leu His Leu Ser Glu Arg Gln
625 630 635 640

Asn Arg Ser Val Arg Leu Thr Trp Glu Ala Gly Ala Asp His Asn Ser
645 650 655

Asn Ile Ser Glu Tyr Ile Val Glu Phe Glu Gly Asn Lys Glu Glu Pro
660 665 670

Gly Arg Trp Glu Glu Leu Thr Arg Val Gln Gly Lys Lys Thr Thr Val
675 680 685

Ile Leu Pro Leu Ala Pro Phe Val Arg Tyr Gln Phe Arg Val Ile Ala
690 695 700

Val Asn Glu Val Gly Arg Ser Gln Pro Ser Gln Pro Ser Asp His His
705 710 715 720

Glu Thr Pro Pro Ala Ala Pro Asp Arg Asn Pro Gln Asn Ile Arg Val
725 730 735

Gln Ala Ser Gln Pro Lys Glu Met Ile Ile Lys Trp Glu Pro Leu Lys
740 745 750

Ser Met Glu Gln Asn Gly Pro Gly Leu Glu Tyr Arg Val Thr Trp Lys
755 760 765

Pro Gln Gly Ala Pro Val Glu Trp Glu Glu Glu Thr Val Thr Asn His
770 775 780

Thr Leu Arg Val Met Thr Pro Ala Val Tyr Ala Pro Tyr Asp Val Lys
785 790 795 800

Val Gln Ala Ile Asn Gln Leu Gly Ser Gly Pro Asp Pro Gln Ser Val
805 810 815

Thr Leu Tyr Ser Gly Glu Asp Tyr Pro Asp Thr Ala Pro Val Ile His
820 825 830

Gly Val Asp Val Ile Asn Ser Thr Leu Val Lys Val Thr Trp Ser Thr
835 840 845

Val Pro Lys Asp Arg Val His Gly Arg Leu Lys Gly Tyr Gln Ile Asn
850 855 860

Trp Trp Lys Thr Lys Ser Leu Leu Asp Gly Arg Thr His Pro Lys Glu
865 870 875 880

Val Asn Ile Leu Arg Phe Ser Gly Gln Arg Asn Ser Gly Met Val Pro
885 890 895

Ser Leu Asp Ala Phe Ser Glu Phe His Leu Thr Val Leu Ala Tyr Asn
900 905 910

Ser Lys Gly Ala Gly Pro Glu Ser Glu Pro Tyr Ile Phe Gln Thr Pro
915 920 925

Glu Gly Val Pro Glu Gln Pro Thr Phe Leu Lys Val Ile Lys Val Asp
930 935 940

Lys Asp Thr Ala Thr Leu Ser Trp Gly Leu Pro Lys Lys Leu Asn Gly
945 950 955 960

Asn Leu Thr Gly Tyr Leu Leu Gln Tyr Gln Ile Ile Asn Asp Thr Tyr
965 970 975

Glu Ile Gly Glu Leu Asn Asp Ile Asn Ile Thr Thr Pro Ser Lys Pro
980 985 990

Ser Trp His Leu Ser Asn Leu Asn Ala Thr Thr Lys Tyr Lys Phe Tyr
995 1000 1005

Leu Arg Ala Cys Thr Ser Gln Gly Cys Gly Lys Pro Ile Thr Glu
1010 1015 1020

Glu Ser Ser Thr Leu Gly Glu Gly Ser Lys Gly Ile Gly Lys Ile
1025 1030 1035

Ser Gly Val Asn Leu Thr Gln Lys Thr His Pro Val Glu Val Phe
1040 1045 1050

Glu Pro Gly Ala Glu His Ile Val Arg Leu Met Thr Lys Asn Trp
1055 1060 1065

Gly Asp Asn Asp Ser Ile Phe Gln Asp Val Ile Glu Thr Arg Gly
1070 1075 1080

Arg Glu Tyr Ala Gly Leu Tyr Asp Asp Ile Ser Thr Gln Gly Trp
1085 1090 1095

Phe Ile Gly Leu Met Cys Ala Ile Ala Leu Leu Thr Leu Leu Leu
1100 1105 1110

Leu Thr Val Cys Phe Val Lys Arg Asn Arg Gly Gly Lys Tyr Ser
1115 1120 1125

Val Lys Glu Lys Glu Asp Leu His Pro Asp Pro Glu Ile Gln Ser
1130 1135 1140

Val Lys Asp Glu Thr Phe Gly Glu Tyr Ser Asp Ser Asp Glu Lys
1145 1150 1155

Pro Leu Lys Gly Ser Leu Arg Ser Leu Asn Arg Asp Met Gln Pro
1160 1165 1170

Thr Glu Ser Ala Asp Ser Leu Val Glu Tyr Gly Glu Gly Asp His
1175 1180 1185

Gly Leu Phe Ser Glu Asp Gly Ser Phe Ile Gly Ala Tyr Ala Gly
1190 1195 1200

Ser Lys Glu Lys Gly Ser Val Glu Ser Asn Gly Ser Ser Thr Ala
1205 1210 1215

Thr Phe Pro Leu Arg Ala
1220

<210> 35
<211> 1253
<212> PRT
<213> Homo sapiens

<400> 35

Met Val Val Ala Leu Arg Tyr Val Trp Pro Leu Leu Leu Cys Ser Pro
1 5 10 15

Cys Leu Leu Ile Gln Ile Pro Glu Glu Tyr Glu Gly His His Val Met
20 25 30

Glu Pro Pro Val Ile Thr Glu Gln Ser Pro Arg Arg Leu Val Val Phe
35 40 45

Pro Thr Asp Asp Ile Ser Leu Lys Cys Glu Ala Ser Gly Lys Pro Glu
50 55 60

Val Gln Phe Arg Trp Thr Arg Asp Gly Val His Phe Lys Pro Lys Glu
65 70 75 80

Glu Leu Gly Val Thr Val Tyr Gln Ser Pro His Ser Gly Ser Phe Thr
85 90 95

Ile Thr Gly Asn Asn Ser Asn Phe Ala Gln Arg Phe Gln Gly Ile Tyr
100 105 110

Arg Cys Phe Ala Ser Asn Lys Leu Gly Thr Ala Met Ser His Glu Ile

115 120 125

Arg Leu Met Ala Glu Gly Ala Pro Lys Trp Pro Lys Glu Thr Val Lys
130 135 140

Pro Val Glu Val Glu Glu Gly Glu Ser Val Val Leu Pro Cys Asn Pro
145 150 155 160

Pro Pro Ser Ala Glu Pro Leu Arg Ile Tyr Trp Met Asn Ser Lys Ile
165 170 175

Leu His Ile Lys Gln Asp Glu Arg Val Thr Met Gly Gln Asn Gly Asn
180 185 190

Leu Tyr Phe Ala Asn Val Leu Thr Ser Asp Asn His Ser Asp Tyr Ile
195 200 205

Cys His Ala His Phe Pro Gly Thr Arg Thr Ile Ile Gln Lys Glu Pro
210 215 220

Ile Asp Leu Arg Val Lys Ala Thr Asn Ser Met Ile Asp Arg Lys Pro
225 230 235 240

Arg Leu Leu Phe Pro Thr Asn Ser Ser Ser His Leu Val Ala Leu Gln
245 250 255

Gly Gln Pro Leu Val Leu Glu Cys Ile Ala Glu Gly Phe Pro Thr Pro
260 265 270

Thr Ile Lys Trp Leu Arg Pro Ser Gly Pro Met Pro Ala Asp Arg Val
275 280 285

Thr Tyr Gln Asn His Asn Lys Thr Leu Gln Leu Leu Lys Val Gly Glu
290 295 300

Glu Asp Asp Gly Glu Tyr Arg Cys Leu Ala Glu Asn Ser Leu Gly Ser
305 310 315 320

Ala Arg His Ala Tyr Tyr Val Thr Val Glu Ala Ala Pro Tyr Trp Leu
325 330 335

His Lys Pro Gln Ser His Leu Tyr Gly Pro Gly Glu Thr Ala Arg Leu
340 345 350

Asp Cys Gln Val Gln Gly Arg Pro Gln Pro Glu Val Thr Trp Arg Ile
355 360 365

Asn Gly Ile Pro Val Glu Glu Leu Ala Lys Asp Gln Lys Tyr Arg Ile
370 375 380

Gln Arg Gly Ala Leu Ile Leu Ser Asn Val Gln Pro Ser Asp Thr Met
385 390 395 400

Val Thr Gln Cys Glu Ala Arg Asn Arg His Gly Leu Leu Leu Ala Asn
405 410 415

Ala Tyr Ile Tyr Val Val Gln Leu Pro Ala Lys Ile Leu Thr Ala Asp
420 425 430

Asn Gln Thr Tyr Met Ala Val Gln Gly Ser Thr Ala Tyr Leu Leu Cys
435 440 445

Lys Ala Phe Gly Ala Pro Val Pro Ser Val Gln Trp Leu Asp Glu Asp
450 455 460

Gly Thr Thr Val Leu Gln Asp Glu Arg Phe Phe Pro Tyr Ala Asn Gly
465 470 475 480

Thr Leu Gly Ile Arg Asp Leu Gln Ala Asn Asp Thr Gly Arg Tyr Phe
485 490 495

Cys Leu Ala Ala Asn Asp Gln Asn Asn Val Thr Ile Met Ala Asn Leu
500 505 510

Lys Val Lys Asp Ala Thr Gln Ile Thr Gln Gly Pro Arg Ser Thr Ile
515 520 525

Glu Lys Lys Gly Ser Arg Val Thr Phe Thr Cys Gln Ala Ser Phe Asp
530 535 540

Pro Ser Leu Gln Pro Ser Ile Thr Trp Arg Gly Asp Gly Arg Asp Leu
545 550 555 560

Gln Glu Leu Gly Asp Ser Asp Lys Tyr Phe Ile Glu Asp Gly Arg Leu
565 570 575

Val Ile His Ser Leu Asp Tyr Ser Asp Gln Gly Asn Tyr Ser Cys Val
580 585 590

Ala Ser Thr Glu Leu Asp Val Val Glu Ser Arg Ala Gln Leu Leu Val
595 600 605

Val Gly Ser Pro Gly Pro Val Pro Arg Leu Val Leu Ser Asp Leu His

610 615 620

Leu Leu Thr Gln Ser Gln Val Arg Val Ser Trp Ser Pro Ala Glu Asp
625 630 635 640

His Asn Ala Pro Ile Glu Lys Tyr Asp Ile Glu Phe Glu Asp Lys Glu
645 650 655

Met Ala Pro Glu Lys Trp Tyr Ser Leu Gly Lys Val Pro Gly Asn Gln
660 665 670

Thr Ser Thr Thr Leu Lys Leu Ser Pro Tyr Val His Tyr Thr Phe Arg
675 680 685

Val Thr Ala Ile Asn Lys Tyr Gly Pro Gly Glu Pro Ser Pro Val Ser
690 695 700

Glu Thr Val Val Thr Pro Glu Ala Ala Pro Glu Lys Asn Pro Val Asp
705 710 715 720

Val Lys Gly Glu Gly Asn Glu Thr Thr Asn Met Val Ile Thr Trp Lys
725 730 735

Pro Leu Arg Trp Met Asp Trp Asn Ala Pro Gln Val Gln Tyr Arg Val
740 745 750

Gln Trp Arg Pro Gln Gly Thr Arg Gly Pro Trp Gln Glu Gln Ile Val
755 760 765

Ser Asp Pro Phe Leu Val Val Ser Asn Thr Ser Thr Phe Val Pro Tyr
770 775 780

Glu Ile Lys Val Gln Ala Val Asn Ser Gln Gly Lys Gly Pro Glu Pro
785 790 795 800

Gln Val Thr Ile Gly Tyr Ser Gly Glu Asp Tyr Pro Gln Ala Ile Pro
805 810 815

Glu Leu Glu Gly Ile Glu Ile Leu Asn Ser Ser Ala Val Leu Val Lys
820 825 830

Trp Arg Pro Val Asp Leu Ala Gln Val Lys Gly His Leu Arg Gly Tyr
835 840 845

Asn Val Thr Tyr Trp Arg Glu Gly Ser Gln Arg Lys His Ser Lys Arg
850 855 860

His Ile His Lys Asp His Val Val Val Pro Ala Asn Thr Thr Ser Val
865 870 875 880

Ile Leu Ser Gly Leu Arg Pro Tyr Ser Ser Tyr His Leu Glu Val Gln
885 890 895

Ala Phe Asn Gly Arg Gly Ser Gly Pro Ala Ser Glu Phe Thr Phe Ser
900 905 910

Thr Pro Glu Gly Val Pro Gly His Pro Glu Ala Leu His Leu Glu Cys
915 920 925

Gln Ser Asn Thr Ser Leu Leu Leu Arg Trp Gln Pro Pro Leu Ser His
930 935 940

Asn Gly Val Leu Thr Gly Tyr Val Leu Ser Tyr His Pro Leu Asp Glu
945 950 955 960

Gly Gly Lys Gly Gln Leu Ser Phe Asn Leu Arg Asp Pro Glu Leu Arg
965 970 975

Thr His Asn Leu Thr Asp Leu Ser Pro His Leu Arg Tyr Arg Phe Gln
980 985 990

Leu Gln Ala Thr Thr Lys Glu Gly Pro Gly Glu Ala Ile Val Arg Glu
995 1000 1005

Gly Gly Thr Met Ala Leu Ser Gly Ile Ser Asp Phe Gly Asn Ile
1010 1015 1020

Ser Ala Thr Ala Gly Glu Asn Tyr Ser Val Val Ser Trp Val Pro
1025 1030 1035

Lys Glu Gly Gln Cys Asn Phe Arg Phe His Ile Leu Phe Lys Ala
1040 1045 1050

Leu Gly Glu Glu Lys Gly Gly Ala Ser Leu Ser Pro Gln Tyr Val
1055 1060 1065

Ser Tyr Asn Gln Ser Ser Tyr Thr Gln Trp Asp Leu Gln Pro Asp
1070 1075 1080

Thr Asp Tyr Glu Ile His Leu Phe Lys Glu Arg Met Phe Arg His
1085 1090 1095

Gln Met Ala Val Lys Thr Asn Gly Thr Gly Arg Val Arg Leu Pro

1100 1105 1110

Pro Ala Gly Phe Ala Thr Glu Gly Trp Phe Ile Gly Phe Val Ser
1115 1120 1125

Ala Ile Ile Leu Leu Leu Leu Val Leu Leu Ile Leu Cys Phe Ile
1130 1135 1140

Lys Arg Ser Lys Gly Gly Lys Tyr Ser Val Lys Asp Lys Glu Asp
1145 1150 1155

Thr Gln Val Asp Ser Glu Ala Arg Pro Met Lys Asp Glu Thr Phe
1160 1165 1170

Gly Glu Tyr Ser Asp Asn Glu Glu Lys Ala Phe Gly Ser Ser Gln
1175 1180 1185

Pro Ser Leu Asn Gly Asp Ile Lys Pro Leu Gly Ser Asp Asp Ser
1190 1195 1200

Leu Ala Asp Tyr Gly Gly Ser Val Asp Val Gln Phe Asn Glu Asp
1205 1210 1215

Gly Ser Phe Ile Gly Gln Tyr Ser Gly Lys Lys Glu Lys Glu Ala
1220 1225 1230

Ala Gly Gly Asn Asp Ser Ser Gly Ala Thr Ser Pro Ile Asn Pro
1235 1240 1245

Ala Val Ala Leu Glu
1250

<210> 36
<211> 1066
<212> PRT
<213> Homo sapiens

<400> 36

Met Ala Arg Gln Pro Pro Pro Pro Trp Val His Ala Ala Phe Leu Leu
1 5 10 15

Cys Leu Leu Ser Leu Gly Gly Ala Ile Glu Ile Pro Met Asp Pro Ser
20 25 30

Ile Gln Asn Glu Leu Thr Gln Pro Pro Thr Ile Thr Lys Gln Ser Ala
35 40 45

Lys Asp His Ile Val Asp Pro Arg Asp Asn Ile Leu Ile Glu Cys Glu
50 55 60

Ala Lys Gly Asn Pro Ala Pro Ser Phe His Trp Thr Arg Asn Ser Arg
65 70 75 80

Phe Phe Asn Ile Ala Lys Asp Pro Arg Val Ser Met Arg Arg Arg Ser
85 90 95

Gly Thr Leu Val Ile Asp Phe Arg Ser Gly Gly Arg Pro Glu Glu Tyr
100 105 110

Glu Gly Glu Tyr Gln Cys Phe Ala Arg Asn Lys Phe Gly Thr Ala Leu
115 120 125

Ser Asn Arg Ile Arg Leu Gln Val Ser Lys Ser Pro Leu Trp Pro Lys
130 135 140

Glu Asn Leu Asp Pro Val Val Val Gln Glu Gly Ala Pro Leu Thr Leu
145 150 155 160

Gln Cys Asn Pro Pro Pro Gly Leu Pro Ser Pro Val Ile Phe Trp Met
165 170 175

Ser Ser Ser Met Glu Pro Ile Thr Gln Asp Lys Arg Val Ser Gln Gly
180 185 190

His Asn Gly Asp Leu Tyr Phe Ser Asn Val Met Leu Gln Asp Met Gln
195 200 205

Thr Asp Tyr Ser Cys Asn Ala Arg Phe His Phe Thr His Thr Ile Gln
210 215 220

Gln Lys Asn Pro Phe Thr Leu Lys Val Leu Thr Thr Arg Gly Val Ala
225 230 235 240

Glu Arg Thr Pro Ser Phe Met Tyr Pro Gln Gly Thr Ala Ser Ser Gln
245 250 255

Met Val Leu Arg Gly Met Asp Leu Leu Leu Glu Cys Ile Ala Ser Gly
260 265 270

Val Pro Thr Pro Asp Ile Ala Trp Tyr Lys Lys Gly Gly Asp Leu Pro
275 280 285

Ser Asp Lys Ala Lys Phe Glu Asn Phe Asn Lys Ala Leu Arg Ile Thr
290 295 300

Asn Val Ser Glu Glu Asp Ser Gly Glu Tyr Phe Cys Leu Ala Ser Asn
305   310   315   320

Lys Met Gly Ser Ile Arg His Thr Ile Ser Val Arg Val Lys Ala Ala
                325   330   335

Pro Tyr Trp Leu Asp Glu Pro Lys Asn Leu Ile Leu Ala Pro Gly Glu
            340   345   350

Asp Gly Arg Leu Val Cys Arg Ala Asn Gly Asn Pro Lys Pro Thr Val
        355   360   365

Gln Trp Met Val Asn Gly Glu Pro Leu Gln Ser Ala Pro Pro Asn Pro
    370   375   380

Asn Arg Glu Val Ala Gly Asp Thr Ile Ile Phe Arg Asp Thr Gln Ile
385   390   395   400

Ser Ser Arg Ala Val Tyr Gln Cys Asn Thr Ser Asn Glu His Gly Tyr
                405   410   415

Leu Leu Ala Asn Ala Phe Val Ser Val Leu Asp Val Pro Pro Arg Met
            420   425   430

Leu Ser Pro Arg Asn Gln Leu Ile Arg Val Ile Leu Tyr Asn Arg Thr
        435   440   445

Arg Leu Asp Cys Pro Phe Phe Gly Ser Pro Ile Pro Thr Leu Arg Trp
    450   455   460

Phe Lys Asn Gly Gln Gly Ser Asn Leu Asp Gly Gly Asn Tyr His Val
465   470   475   480

Tyr Glu Asn Gly Ser Leu Glu Ile Lys Met Ile Arg Lys Glu Asp Gln
                485   490   495

Gly Ile Tyr Thr Cys Val Ala Thr Asn Ile Leu Gly Lys Ala Glu Asn
            500   505   510

Gln Val Arg Leu Glu Val Lys Asp Pro Thr Arg Ile Tyr Arg Met Pro
        515   520   525

Glu Asp Gln Val Ala Arg Arg Gly Thr Thr Val Gln Leu Glu Cys Arg
    530   535   540

Val Lys His Asp Pro Ser Leu Lys Leu Thr Val Ser Trp Leu Lys Asp
545 550 555 560

Asp Glu Pro Leu Tyr Ile Gly Asn Arg Met Lys Lys Glu Asp Asp Ser
565 570 575

Leu Thr Ile Phe Gly Val Ala Glu Arg Asp Gln Gly Ser Tyr Thr Cys
580 585 590

Val Ala Ser Thr Glu Leu Asp Gln Asp Leu Ala Lys Ala Tyr Leu Thr
595 600 605

Val Leu Ala Asp Gln Ala Thr Pro Thr Asn Arg Leu Ala Ala Leu Pro
610 615 620

Lys Gly Arg Pro Asp Arg Pro Arg Asp Leu Glu Leu Thr Asp Leu Ala
625 630 635 640

Glu Arg Ser Val Arg Leu Thr Trp Ile Pro Gly Asp Ala Asn Asn Ser
645 650 655

Pro Ile Thr Asp Tyr Val Val Gln Phe Glu Glu Asp Gln Phe Gln Pro
660 665 670

Gly Val Trp His Asp His Ser Lys Tyr Pro Gly Ser Val Asn Ser Ala
675 680 685

Val Leu Arg Leu Ser Pro Tyr Val Asn Tyr Gln Phe Arg Val Ile Ala
690 695 700

Ile Asn Glu Val Gly Ser Ser His Pro Ser Leu Pro Ser Glu Arg Tyr
705 710 715 720

Arg Thr Ser Gly Ala Pro Pro Glu Ser Asn Pro Gly Asp Val Lys Gly
725 730 735

Glu Gly Thr Arg Lys Asn Asn Met Glu Ile Thr Trp Thr Pro Met Asn
740 745 750

Ala Thr Ser Ala Phe Gly Pro Asn Leu Arg Tyr Ile Val Lys Trp Arg
755 760 765

Arg Arg Glu Thr Arg Glu Ala Trp Asn Asn Val Thr Val Trp Gly Ser
770 775 780

Arg Tyr Val Val Gly Gln Thr Pro Val Tyr Val Pro Tyr Glu Ile Arg
785 790 795 800

Val Gln Ala Glu Asn Asp Phe Gly Lys Gly Pro Glu Pro Glu Ser Val
805 810 815

Ile Gly Tyr Ser Gly Glu Asp Leu Pro Ser Ala Pro Arg Arg Phe Arg
820 825 830

Val Arg Gln Pro Asn Leu Glu Thr Ile Asn Leu Glu Trp Asp His Pro
835 840 845

Glu His Pro Asn Gly Ile Met Ile Gly Tyr Thr Leu Lys Tyr Val Ala
850 855 860

Phe Asn Gly Thr Lys Val Gly Lys Gln Ile Val Glu Asn Phe Ser Pro
865 870 875 880

Asn Gln Thr Lys Phe Thr Val Gln Arg Thr Asp Pro Val Ser Arg Tyr
885 890 895

Arg Phe Thr Leu Ser Ala Arg Thr Gln Val Gly Ser Gly Glu Ala Val
900 905 910

Thr Glu Glu Ser Pro Ala Pro Pro Asn Glu Ala Tyr Thr Asn Asn Gln
915 920 925

Ala Asp Ile Ala Thr Gln Gly Trp Phe Ile Gly Leu Met Cys Ala Ile
930 935 940

Ala Leu Leu Val Leu Ile Leu Leu Ile Val Cys Phe Ile Lys Arg Ser
945 950 955 960

Arg Gly Gly Lys Tyr Pro Val Arg Glu Lys Lys Asp Val Pro Leu Gly
965 970 975

Pro Glu Asp Pro Lys Glu Glu Asp Gly Ser Phe Asp Tyr Ser Asp Glu
980 985 990

Asp Asn Lys Pro Leu Gln Gly Ser Gln Thr Ser Leu Asp Gly Thr Ile
995 1000 1005

Lys Gln Gln Glu Ser Asp Asp Ser Leu Val Asp Tyr Gly Glu Gly
1010 1015 1020

Gly Glu Gly Gln Phe Asn Glu Asp Gly Ser Phe Ile Gly Gln Tyr
1025 1030 1035

Thr Val Lys Lys Asp Lys Glu Glu Thr Glu Gly Asn Glu Ser Ser
1040 1045 1050

Glu Ala Thr Ser Pro Val Asn Ala Ile Tyr Ser Leu Ala
1055 1060 1065

<210> 37
<211> 280
<212> PRT
<213> Homo sapiens

<400> 37

Met Lys Phe Arg Ala Lys Ile Val Asp Gly Ala Cys Leu Asn His Phe
1 5 10 15

Thr Arg Ile Ser Asn Met Ile Ala Lys Leu Ala Lys Thr Cys Thr Leu
20 25 30

Arg Ile Ser Pro Asp Lys Leu Asn Phe Ile Leu Cys Asp Lys Leu Ala
35 40 45

Asn Gly Gly Val Ser Met Trp Cys Glu Leu Glu Gln Glu Asn Phe Phe
50 55 60

Asn Glu Phe Gln Met Glu Gly Val Ser Ala Glu Asn Asn Glu Ile Tyr
65 70 75 80

Leu Glu Leu Thr Ser Glu Asn Leu Ser Arg Ala Leu Lys Thr Ala Gln
85 90 95

Asn Ala Arg Ala Leu Lys Ile Lys Leu Thr Asn Lys His Phe Pro Cys
100 105 110

Leu Thr Val Ser Val Glu Leu Leu Ser Met Ser Ser Ser Ser Arg Ile
115 120 125

Val Thr His Asp Ile Pro Ile Lys Val Ile Pro Arg Lys Leu Trp Lys
130 135 140

Asp Leu Gln Glu Pro Val Val Pro Asp Pro Asp Val Ser Ile Tyr Leu
145 150 155 160

Pro Val Leu Lys Thr Met Lys Ser Val Val Glu Lys Met Lys Asn Ile
165 170 175

Ser Asn His Leu Val Ile Glu Ala Asn Leu Asp Gly Glu Leu Asn Leu
180 185 190

Lys Ile Glu Thr Glu Leu Val Cys Val Thr Thr His Phe Lys Asp Leu
195 200 205

Gly Asn Pro Pro Leu Ala Ser Glu Ser Thr His Glu Asp Arg Asn Val
210 215 220

Glu His Met Ala Glu Val His Ile Asp Ile Arg Lys Leu Leu Gln Phe
225 230 235 240

Leu Ala Gly Gln Gln Val Asn Pro Thr Lys Ala Leu Cys Asn Ile Val
245 250 255

Asn Asn Lys Met Val His Phe Asp Leu Leu His Glu Asp Val Ser Leu
260 265 270

Gln Tyr Phe Ile Pro Ala Leu Ser
275 280

<210> 38
<211> 278
<212> PRT
<213> Homo sapiens

<400> 38

Met Lys Phe Arg Ala Lys Ile Thr Gly Lys Gly Cys Leu Glu Leu Phe
1 5 10 15

Ile His Val Ser Gly Thr Val Ala Arg Leu Ala Lys Val Cys Val Leu
20 25 30

Arg Val Arg Pro Asp Ser Leu Cys Phe Gly Pro Ala Gly Ser Gly Gly
35 40 45

Leu His Glu Ala Arg Leu Trp Cys Glu Val Arg Gln Gly Ala Phe Gln
50 55 60

Gln Phe Arg Met Glu Gly Val Ser Glu Asp Leu Asp Glu Ile His Leu
65 70 75 80

Glu Leu Thr Ala Glu His Leu Ser Arg Ala Ala Arg Ser Ala Ala Gly
85 90 95

Ala Ser Ser Leu Lys Leu Gln Leu Thr His Lys Arg Arg Pro Ser Leu
100 105 110

Thr Val Ala Val Glu Leu Val Ser Ser Leu Gly Arg Ala Arg Ser Val
115 120 125

Val His Asp Leu Pro Val Arg Val Leu Pro Arg Arg Val Trp Arg Asp
    130   135   140

Cys Leu Pro Pro Ser Leu Arg Ala Ser Asp Ala Ser Ile Arg Leu Pro
145   150   155   160

Arg Trp Arg Thr Leu Arg Ser Ile Val Glu Arg Met Ala Asn Val Gly
                165   170   175

Ser His Val Leu Val Glu Ala Asn Leu Ser Gly Arg Met Thr Leu Ser
            180   185   190

Ile Glu Thr Glu Val Val Ser Ile Gln Ser Tyr Phe Lys Asn Leu Gly
        195   200   205

Asn Pro Pro Gln Ser Ala Val Gly Val Pro Glu Asn Arg Asp Leu Glu
    210   215   220

Ser Met Val Gln Val Arg Val Asp Asn Arg Lys Leu Leu Gln Phe Leu
225   230   235   240

Glu Gly Gln Gln Ile His Pro Thr Thr Ala Leu Cys Asn Ile Trp Asp
                245   250   255

Asn Thr Leu Leu Gln Leu Val Leu Val Gln Glu Tyr Val Ser Leu Gln
            260   265   270

Tyr Phe Ile Pro Ala Leu
        275

<210> 39
<211> 1844
<212> PRT
<213> Homo sapiens

<400> 39

Met Val Gly Val Leu Ala Met Ala Ala Ala Ala Ala Pro Pro Pro Val
1   5   10   15

Lys Asp Cys Glu Ile Glu Pro Cys Lys Lys Arg Lys Lys Asp Asp Asp
            20   25   30

Thr Ser Thr Cys Lys Thr Ile Thr Lys Tyr Leu Ser Pro Leu Gly Lys
        35   40   45

Thr Arg Asp Arg Val Phe Ala Pro Pro Lys Pro Ser Asn Ile Leu Asp

50 55 60

Tyr Phe Arg Lys Thr Ser Pro Thr Asn Glu Lys Thr Gln Leu Gly Lys
65 70 75 80

Glu Cys Lys Ile Lys Ser Pro Glu Ser Val Pro Val Asp Ser Asn Lys
85 90 95

Asp Cys Thr Thr Pro Leu Glu Met Phe Ser Asn Val Glu Phe Lys Lys
100 105 110

Lys Arg Lys Arg Val Asn Leu Ser His Gln Leu Asn Asn Ile Lys Thr
115 120 125

Glu Asn Glu Ala Pro Ile Glu Ile Ser Ser Asp Asp Ser Lys Glu Asp
130 135 140

Tyr Ser Leu Asn Asn Asp Phe Val Glu Ser Ser Thr Ser Val Leu Arg
145 150 155 160

Tyr Lys Lys Gln Val Glu Val Leu Ala Glu Asn Ile Gln Asp Thr Lys
165 170 175

Ser Gln Pro Asn Thr Met Thr Ser Leu Gln Asn Ser Lys Lys Val Asn
180 185 190

Pro Lys Gln Gly Thr Thr Lys Asn Asp Phe Lys Lys Leu Arg Lys Arg
195 200 205

Lys Cys Arg Asp Val Val Asp Leu Ser Glu Ser Leu Pro Leu Ala Glu
210 215 220

Glu Leu Asn Leu Leu Lys Lys Asp Gly Lys Asp Thr Lys Gln Met Glu
225 230 235 240

Asn Thr Thr Ser His Ala Asn Ser Arg Asp Asn Val Thr Glu Ala Ala
245 250 255

Gln Leu Asn Asp Ser Ile Ile Thr Val Ser Tyr Glu Glu Phe Leu Lys
260 265 270

Ser His Lys Glu Asn Lys Val Glu Glu Ile Pro Asp Ser Thr Met Ser
275 280 285

Ile Cys Val Pro Ser Glu Thr Val Asp Glu Ile Val Lys Ser Gly Tyr
290 295 300

Ile Ser Glu Ser Glu Asn Ser Glu Ile Ser Gln Gln Val Arg Phe Lys
305 310 315 320

Thr Val Thr Val Leu Ala Gln Val His Pro Ile Pro Pro Lys Lys Thr
325 330 335

Gly Lys Ile Pro Arg Ile Phe Leu Lys Gln Lys Gln Phe Glu Met Glu
340 345 350

Asn Ser Leu Ser Asp Pro Glu Asn Glu Gln Thr Val Gln Lys Arg Lys
355 360 365

Ser Asn Val Val Ile Gln Glu Glu Glu Leu Glu Leu Ala Val Leu Glu
370 375 380

Ala Gly Ser Ser Glu Ala Val Lys Pro Lys Cys Thr Leu Glu Glu Arg
385 390 395 400

Gln Gln Phe Met Lys Ala Phe Arg Gln Pro Ala Ser Asp Ala Leu Lys
405 410 415

Asn Gly Val Lys Lys Ser Ser Asp Lys Gln Lys Asp Leu Asn Glu Lys
420 425 430

Cys Leu Tyr Glu Val Gly Arg Asp Asp Asn Ser Lys Lys Ile Met Glu
435 440 445

Asn Ser Gly Ile Gln Met Val Ser Lys Asn Gly Asn Leu Gln Leu His
450 455 460

Thr Asp Lys Gly Ser Phe Leu Lys Glu Lys Asn Lys Lys Leu Lys Lys
465 470 475 480

Lys Asn Lys Lys Thr Leu Asp Thr Gly Ala Ile Pro Gly Lys Asn Arg
485 490 495

Glu Gly Asn Thr Gln Lys Lys Glu Thr Thr Phe Phe Leu Lys Glu Lys
500 505 510

Gln Tyr Gln Asn Arg Met Ser Leu Arg Gln Arg Lys Thr Glu Phe Phe
515 520 525

Lys Ser Ser Thr Leu Phe Asn Asn Glu Ser Leu Val Tyr Glu Asp Ile
530 535 540

Ala Asn Asp Asp Leu Leu Lys Val Ser Ser Leu Cys Asn Asn Asn Lys

545 550 555 560

Leu Ser Arg Lys Thr Ser Ile Pro Val Lys Asp Ile Lys Leu Thr Gln
565 570 575

Ser Lys Ala Glu Ser Glu Ala Ser Leu Leu Asn Val Ser Thr Pro Lys
580 585 590

Ser Thr Arg Arg Ser Gly Arg Ile Ser Ser Thr Pro Thr Thr Glu Thr
595 600 605

Ile Arg Gly Ile Asp Ser Asp Asp Val Gln Asp Asn Ser Gln Leu Lys
610 615 620

Ala Ser Thr Gln Lys Ala Ala Asn Leu Ser Glu Lys His Ser Leu Tyr
625 630 635 640

Thr Ala Glu Leu Ile Thr Val Pro Phe Asp Ser Glu Ser Pro Ile Arg
645 650 655

Met Lys Phe Thr Arg Ile Ser Thr Pro Lys Lys Ser Lys Lys Lys Ser
660 665 670

Asn Lys Arg Ser Glu Lys Ser Glu Ala Thr Asp Gly Gly Phe Thr Ser
675 680 685

Gln Ile Arg Lys Ala Ser Asn Thr Ser Lys Asn Ile Ser Lys Ala Lys
690 695 700

Gln Leu Ile Glu Lys Ala Lys Ala Leu His Ile Ser Arg Ser Lys Val
705 710 715 720

Thr Glu Glu Ile Ala Ile Pro Leu Arg Arg Ser Ser Arg His Gln Thr
725 730 735

Leu Pro Glu Arg Lys Lys Leu Ser Glu Thr Glu Asp Ser Val Ile Ile
740 745 750

Ile Asp Ser Ser Pro Thr Ala Leu Lys His Pro Glu Lys Asn Gln Lys
755 760 765

Lys Leu Gln Cys Leu Asn Asp Val Leu Gly Lys Lys Leu Asn Thr Ser
770 775 780

Thr Lys Asn Val Pro Gly Lys Met Lys Val Ala Pro Leu Phe Leu Val
785 790 795 800

Arg Lys Ala Gln Lys Ala Ala Asp Pro Val Pro Ser Phe Asp Glu Ser
805 810 815

Ser Gln Asp Thr Ser Glu Lys Ser Gln Asp Cys Asp Val Gln Cys Lys
820 825 830

Ala Lys Arg Asp Phe Leu Met Ser Gly Leu Pro Asp Leu Leu Lys Arg
835 840 845

Gln Ile Ala Lys Lys Ala Ala Ala Leu Asp Val Tyr Asn Ala Val Ser
850 855 860

Thr Ser Phe Gln Arg Val Val His Val Gln Gln Lys Asp Asp Gly Cys
865 870 875 880

Cys Leu Trp His Leu Lys Pro Pro Ser Cys Pro Leu Leu Thr Lys Phe
885 890 895

Lys Glu Leu Asn Thr Lys Val Ile Asp Leu Ser Lys Cys Gly Ile Ala
900 905 910

Leu Gly Glu Phe Ser Thr Leu Asn Ser Lys Leu Lys Ser Gly Asn Ser
915 920 925

Ala Ala Val Phe Met Arg Thr Arg Lys Glu Phe Thr Glu Glu Val Arg
930 935 940

Asn Leu Leu Leu Glu Glu Ile Arg Trp Ser Asn Pro Glu Phe Ser Leu
945 950 955 960

Lys Lys Tyr Phe Pro Leu Leu Leu Lys Lys Gln Ile Glu His Gln Val
965 970 975

Leu Ser Ser Glu Cys His Ser Lys Gln Glu Leu Glu Ala Asp Val Ser
980 985 990

His Lys Glu Thr Lys Arg Lys Leu Val Glu Ala Glu Asn Ser Lys Ser
995 1000 1005

Lys Arg Lys Lys Pro Asn Glu Tyr Ser Lys Asn Leu Glu Lys Thr
1010 1015 1020

Asn Arg Lys Ser Glu Glu Leu Ser Lys Arg Asn Asn Ser Ser Gly
1025 1030 1035

Ile Lys Leu Asp Ser Ser Lys Asp Ser Gly Thr Glu Asp Met Leu

1040 1045 1050

Trp Thr Glu Lys Tyr Gln Pro Gln Thr Ala Ser Glu Leu Ile Gly
1055 1060 1065

Asn Glu Leu Ala Ile Lys Lys Leu His Ser Trp Leu Lys Asp Trp
1070 1075 1080

Lys Arg Arg Ala Glu Leu Glu Glu Arg Gln Asn Leu Lys Gly Lys
1085 1090 1095

Arg Asp Glu Lys His Glu Asp Phe Ser Gly Gly Ile Asp Phe Lys
1100 1105 1110

Gly Ser Ser Asp Asp Glu Glu Glu Ser Arg Leu Cys Asn Thr Val
1115 1120 1125

Leu Ile Thr Gly Pro Thr Gly Val Gly Lys Thr Ala Ala Val Tyr
1130 1135 1140

Ala Cys Ala Gln Glu Leu Gly Phe Lys Ile Phe Glu Val Asn Ala
1145 1150 1155

Ser Ser Gln Arg Ser Gly Arg Gln Ile Leu Ser Gln Leu Lys Glu
1160 1165 1170

Ala Thr Gln Ser His Gln Val Asp Lys Gln Gly Val Asn Ser Gln
1175 1180 1185

Lys Pro Cys Phe Phe Asn Ser Tyr Tyr Ile Gly Lys Ser Pro Lys
1190 1195 1200

Lys Ile Ser Ser Pro Lys Lys Val Val Thr Ser Pro Arg Lys Val
1205 1210 1215

Pro Pro Pro Ser Pro Lys Ser Ser Gly Pro Lys Arg Ala Leu Pro
1220 1225 1230

Pro Lys Thr Leu Ala Asn Tyr Phe Lys Val Ser Pro Lys Pro Lys
1235 1240 1245

Asn Asn Glu Glu Ile Gly Met Leu Leu Glu Asn Asn Lys Gly Ile
1250 1255 1260

Lys Asn Ser Phe Glu Gln Lys Gln Ile Thr Gln Thr Lys Ser Thr
1265 1270 1275

Asn Ala Thr Asn Ser Asn Val Lys Asp Val Gly Ala Glu Glu Pro
1280 1285 1290

Ser Arg Lys Asn Ala Thr Ser Leu Ile Leu Phe Glu Glu Val Asp
1295 1300 1305

Val Ile Phe Asp Glu Asp Ala Gly Phe Leu Asn Ala Ile Lys Thr
1310 1315 1320

Phe Met Ala Thr Thr Lys Arg Pro Val Ile Leu Thr Thr Ser Asp
1325 1330 1335

Pro Thr Phe Ser Leu Met Phe Asp Gly Cys Phe Glu Glu Ile Lys
1340 1345 1350

Phe Ser Thr Pro Ser Leu Leu Asn Val Ala Ser Tyr Leu Gln Met
1355 1360 1365

Ile Cys Leu Thr Glu Asn Phe Arg Thr Asp Val Lys Asp Phe Val
1370 1375 1380

Thr Leu Leu Thr Ala Asn Thr Cys Asp Ile Arg Lys Ser Ile Leu
1385 1390 1395

Tyr Leu Gln Phe Trp Ile Arg Ser Gly Gly Gly Val Leu Glu Glu
1400 1405 1410

Arg Pro Leu Thr Leu Tyr Arg Gly Asn Ser Arg Asn Val Gln Leu
1415 1420 1425

Val Cys Ser Glu His Gly Leu Asp Asn Lys Ile Tyr Pro Lys Asn
1430 1435 1440

Thr Lys Lys Lys Arg Val Asp Leu Pro Lys Cys Asp Ser Gly Cys
1445 1450 1455

Ala Glu Thr Leu Phe Gly Leu Lys Asn Ile Phe Ser Pro Ser Glu
1460 1465 1470

Asp Leu Phe Ser Phe Leu Lys His Lys Ile Thr Met Lys Glu Glu
1475 1480 1485

Trp His Lys Phe Ile Gln Leu Leu Thr Glu Phe Gln Met Arg Asn
1490 1495 1500

Val Asp Phe Leu Tyr Ser Asn Leu Glu Phe Ile Leu Pro Leu Pro

1505 1510 1515

Val Asp Thr Ile Pro Glu Thr Lys Asn Phe Cys Gly Pro Ser Val
1520 1525 1530

Thr Val Asp Ala Ser Ala Ala Thr Lys Ser Met Asn Cys Leu Ala
1535 1540 1545

Arg Lys His Ser Glu Arg Glu Gln Pro Leu Lys Lys Ser Gln Lys
1550 1555 1560

Lys Lys Gln Lys Lys Thr Leu Val Ile Leu Asp Asp Ser Asp Leu
1565 1570 1575

Phe Asp Thr Asp Leu Asp Phe Pro Asp Gln Ser Ile Ser Leu Ser
1580 1585 1590

Ser Val Ser Ser Ser Ser Asn Ala Glu Glu Ser Lys Thr Gly Asp
1595 1600 1605

Glu Glu Ser Lys Ala Arg Asp Lys Gly Asn Asn Pro Glu Thr Lys
1610 1615 1620

Lys Ser Ile Pro Cys Pro Pro Lys Thr Thr Ala Gly Lys Lys Cys
1625 1630 1635

Ser Ala Leu Val Ser His Cys Leu Asn Ser Leu Ser Glu Phe Met
1640 1645 1650

Asp Asn Met Ser Phe Leu Asp Ala Leu Leu Thr Asp Val Arg Glu
1655 1660 1665

Gln Asn Lys Tyr Gly Arg Asn Asp Phe Ser Trp Thr Asn Gly Lys
1670 1675 1680

Val Thr Ser Gly Leu Cys Asp Glu Phe Ser Leu Glu Ser Asn Asp
1685 1690 1695

Gly Trp Thr Ser Gln Ser Ser Gly Glu Leu Lys Ala Ala Ala Glu
1700 1705 1710

Ala Leu Ser Phe Thr Lys Cys Ser Ser Ala Ile Ser Lys Ala Leu
1715 1720 1725

Glu Thr Leu Asn Ser Cys Lys Lys Leu Gly Arg Asp Pro Thr Asn
1730 1735 1740

Asp Leu Thr Phe Tyr Val Ser Gln Lys Arg Asn Asn Val Tyr Phe
1745 1750 1755

Ser Gln Ser Ala Ala Asn Leu Asp Asn Ala Trp Lys Arg Ile Ser
1760 1765 1770

Val Ile Lys Ser Val Phe Ser Ser Arg Ser Leu Leu Tyr Val Gly
1775 1780 1785

Asn Arg Gln Ala Ser Ile Ile Glu Tyr Leu Pro Thr Leu Arg Asn
1790 1795 1800

Ile Cys Lys Thr Glu Lys Leu Lys Glu Gln Gly Lys Ser Lys Arg
1805 1810 1815

Arg Phe Leu His Tyr Phe Glu Gly Ile His Leu Asp Ile Pro Lys
1820 1825 1830

Glu Thr Val Asn Thr Leu Ala Ala Asp Phe Pro
1835 1840

<210> 40
<211> 1148
<212> PRT
<213> Homo sapiens

<400> 40

Met Asp Ile Arg Lys Phe Phe Gly Val Ile Pro Ser Gly Lys Lys Leu
1 5 10 15

Val Ser Glu Thr Val Lys Lys Asn Glu Lys Thr Lys Ser Asp Glu Glu
20 25 30

Thr Leu Lys Ala Lys Lys Gly Ile Lys Glu Ile Lys Val Asn Ser Ser
35 40 45

Arg Lys Glu Asp Asp Phe Lys Gln Lys Gln Pro Ser Lys Lys Lys Arg
50 55 60

Ile Ile Tyr Asp Ser Asp Ser Glu Ser Glu Glu Thr Leu Gln Val Lys
65 70 75 80

Asn Ala Lys Lys Pro Pro Glu Lys Leu Pro Val Ser Ser Lys Pro Gly
85 90 95

Lys Ile Ser Arg Gln Asp Pro Val Thr Tyr Ile Ser Glu Thr Asp Glu
100 105 110

Glu Asp Asp Phe Met Cys Lys Lys Ala Ala Ser Lys Ser Lys Glu Asn
115 120 125

Gly Arg Ser Thr Asn Ser His Leu Gly Thr Ser Asn Met Lys Lys Asn
130 135 140

Glu Glu Asn Thr Lys Thr Lys Asn Lys Pro Leu Ser Pro Ile Lys Leu
145 150 155 160

Thr Pro Thr Ser Val Leu Asp Tyr Phe Gly Thr Gly Ser Val Gln Arg
165 170 175

Ser Asn Lys Lys Met Val Ala Ser Lys Arg Lys Glu Leu Ser Gln Asn
180 185 190

Thr Asp Glu Ser Gly Leu Asn Asp Glu Ala Ile Ala Lys Gln Leu Gln
195 200 205

Leu Asp Glu Asp Ala Glu Leu Glu Arg Gln Leu His Glu Asp Glu Glu
210 215 220

Phe Ala Arg Thr Leu Ala Met Leu Asp Glu Glu Pro Lys Thr Lys Lys
225 230 235 240

Ala Arg Lys Asp Thr Glu Ala Gly Glu Thr Phe Ser Ser Val Gln Ala
245 250 255

Asn Leu Ser Lys Ala Glu Lys His Lys Tyr Pro His Lys Val Lys Thr
260 265 270

Ala Gln Val Ser Asp Glu Arg Lys Ser Tyr Ser Pro Arg Lys Gln Ser
275 280 285

Lys Tyr Glu Ser Ser Lys Glu Ser Gln Gln His Ser Lys Ser Ser Ala
290 295 300

Asp Lys Ile Gly Glu Val Ser Ser Pro Lys Ala Ser Ser Lys Leu Ala
305 310 315 320

Ile Met Lys Arg Lys Glu Glu Ser Ser Tyr Lys Glu Ile Glu Pro Val
325 330 335

Ala Ser Lys Arg Lys Glu Asn Ala Ile Lys Leu Lys Gly Glu Thr Lys
340 345 350

Thr Pro Lys Lys Thr Lys Ser Ser Pro Ala Lys Lys Glu Ser Val Ser
355 360 365

Pro Glu Asp Ser Glu Lys Lys Arg Thr Asn Tyr Gln Ala Tyr Arg Ser
370 375 380

Tyr Leu Asn Arg Glu Gly Pro Lys Ala Leu Gly Ser Lys Glu Ile Pro
385 390 395 400

Lys Gly Ala Glu Asn Cys Leu Glu Gly Leu Ile Phe Val Ile Thr Gly
405 410 415

Val Leu Glu Ser Ile Glu Arg Asp Glu Ala Lys Ser Leu Ile Glu Arg
420 425 430

Tyr Gly Gly Lys Val Thr Gly Asn Val Ser Lys Lys Thr Asn Tyr Leu
435 440 445

Val Met Gly Arg Asp Ser Gly Gln Ser Lys Ser Asp Lys Ala Ala Ala
450 455 460

Leu Gly Thr Lys Ile Ile Asp Glu Asp Gly Leu Leu Asn Leu Ile Arg
465 470 475 480

Thr Met Pro Gly Lys Lys Ser Lys Tyr Glu Ile Ala Val Glu Thr Glu
485 490 495

Met Lys Lys Glu Ser Lys Leu Glu Arg Thr Pro Gln Lys Asn Val Gln
500 505 510

Gly Lys Arg Lys Ile Ser Pro Ser Lys Lys Glu Ser Glu Ser Lys Lys
515 520 525

Ser Arg Pro Thr Ser Lys Arg Asp Ser Leu Ala Lys Thr Ile Lys Lys
530 535 540

Glu Thr Asp Val Phe Trp Lys Ser Leu Asp Phe Lys Glu Gln Val Ala
545 550 555 560

Glu Glu Thr Ser Gly Asp Ser Lys Ala Arg Asn Leu Ala Asp Asp Ser
565 570 575

Ser Glu Asn Lys Val Glu Asn Leu Leu Trp Val Asp Lys Tyr Lys Pro
580 585 590

Thr Ser Leu Lys Thr Ile Ile Gly Gln Gln Gly Asp Gln Ser Cys Ala
595 600 605

Asn Lys Leu Leu Arg Trp Leu Arg Asn Trp Gln Lys Ser Ser Ser Glu
610 615 620

Asp Lys Lys His Ala Ala Lys Phe Gly Lys Phe Ser Gly Lys Asp Asp
625 630 635 640

Gly Ser Ser Phe Lys Ala Ala Leu Leu Ser Gly Pro Pro Gly Val Gly
645 650 655

Lys Thr Thr Thr Ala Ser Leu Val Cys Gln Glu Leu Gly Tyr Ser Tyr
660 665 670

Val Glu Leu Asn Ala Ser Asp Thr Arg Ser Lys Ser Ser Leu Lys Ala
675 680 685

Ile Val Ala Glu Ser Leu Asn Asn Thr Ser Ile Lys Gly Phe Tyr Ser
690 695 700

Asn Gly Ala Ala Ser Ser Val Ser Thr Lys His Ala Leu Ile Met Asp
705 710 715 720

Glu Val Asp Gly Met Ala Gly Asn Glu Asp Arg Gly Gly Ile Gln Glu
725 730 735

Leu Ile Gly Leu Ile Lys His Thr Lys Ile Pro Ile Ile Cys Met Cys
740 745 750

Asn Asp Arg Asn His Pro Lys Ile Arg Ser Leu Val His Tyr Cys Phe
755 760 765

Asp Leu Arg Phe Gln Arg Pro Arg Val Glu Gln Ile Lys Gly Ala Met
770 775 780

Met Ser Ile Ala Phe Lys Glu Gly Leu Lys Ile Pro Pro Pro Ala Met
785 790 795 800

Asn Glu Ile Ile Leu Gly Ala Asn Gln Asp Ile Arg Gln Val Leu His
805 810 815

Asn Leu Ser Met Trp Cys Ala Arg Ser Lys Ala Leu Thr Tyr Asp Gln
820 825 830

Ala Lys Ala Asp Ser His Arg Ala Lys Lys Asp Ile Lys Met Gly Pro
835 840 845

Phe Asp Val Ala Arg Lys Val Phe Ala Ala Gly Glu Glu Thr Ala His
    850   855   860

Met Ser Leu Val Asp Lys Ser Asp Leu Phe Phe His Asp Tyr Ser Ile
865   870   875   880

Ala Pro Leu Phe Val Gln Glu Asn Tyr Ile His Val Lys Pro Val Ala
                885   890   895

Ala Gly Gly Asp Met Lys Lys His Leu Met Leu Leu Ser Arg Ala Ala
            900   905   910

Asp Ser Ile Cys Asp Gly Asp Leu Val Asp Ser Gln Ile Arg Ser Lys
        915   920   925

Gln Asn Trp Ser Leu Leu Pro Ala Gln Ala Ile Tyr Ala Ser Val Leu
    930   935   940

Pro Gly Glu Leu Met Arg Gly Tyr Met Thr Gln Phe Pro Thr Phe Pro
945   950   955   960

Ser Trp Leu Gly Lys His Ser Ser Thr Gly Lys His Asp Arg Ile Val
                965   970   975

Gln Asp Leu Ala Leu His Met Ser Leu Arg Thr Tyr Ser Ser Lys Arg
            980   985   990

Thr Val Asn Met Asp Tyr Leu Ser Leu Leu Arg Asp Ala Leu Val Gln
        995   1000   1005

Pro Leu Thr Ser Gln Gly Val Asp Gly Val Gln Asp Val Val Ala
    1010   1015   1020

Leu Met Asp Thr Tyr Tyr Leu Met Lys Glu Asp Phe Glu Asn Ile
    1025   1030   1035

Met Glu Ile Ser Ser Trp Gly Gly Lys Pro Ser Pro Phe Ser Lys
    1040   1045   1050

Leu Asp Pro Lys Val Lys Ala Ala Phe Thr Arg Ala Tyr Asn Lys
    1055   1060   1065

Glu Ala His Leu Thr Pro Tyr Ser Leu Gln Ala Ile Lys Ala Ser
    1070   1075   1080

Arg His Ser Thr Ser Pro Ser Leu Asp Ser Glu Tyr Asn Glu Glu
    1085   1090   1095

Leu Asn Glu Asp Asp Ser Gln Ser Asp Glu Lys Asp Gln Asp Ala
    1100   1105   1110

Ile Glu Thr Asp Ala Met Ile Lys Lys Lys Thr Lys Ser Ser Lys
    1115   1120   1125

Pro Ser Lys Pro Glu Lys Asp Lys Glu Pro Arg Lys Gly Lys Gly
    1130   1135   1140

Lys Ser Ser Lys Lys
    1145

<210> 41
<211> 307
<212> PRT
<213> Homo sapiens

<400> 41

Met Ala Glu Ile Ser Asp Leu Asp Arg Gln Ile Glu Gln Leu Arg Arg
1   5   10   15

Cys Glu Leu Ile Lys Glu Ser Glu Val Lys Ala Leu Cys Ala Lys Ala
            20   25   30

Arg Glu Ile Leu Val Glu Glu Ser Asn Val Gln Arg Val Asp Ser Pro
        35   40   45

Val Thr Val Cys Gly Asp Ile His Gly Gln Phe Tyr Asp Leu Lys Glu
    50   55   60

Leu Phe Arg Val Gly Gly Asp Val Pro Glu Thr Asn Tyr Leu Phe Met
65   70   75   80

Gly Asp Phe Val Asp Arg Gly Phe Tyr Ser Val Glu Thr Phe Leu Leu
                85   90   95

Leu Leu Ala Leu Lys Val Arg Tyr Pro Asp Arg Ile Thr Leu Ile Arg
            100   105   110

Gly Asn His Glu Ser Arg Gln Ile Thr Gln Val Tyr Gly Phe Tyr Asp
        115   120   125

Glu Cys Leu Arg Lys Tyr Gly Ser Val Thr Val Trp Arg Tyr Cys Thr
    130   135   140

Glu Ile Phe Asp Tyr Leu Ser Leu Ser Ala Ile Ile Asp Gly Lys Ile

145 150 155 160

Phe Cys Val His Gly Gly Leu Ser Pro Ser Ile Gln Thr Leu Asp Gln
165 170 175

Ile Arg Thr Ile Asp Arg Lys Gln Glu Val Pro His Asp Gly Pro Met
180 185 190

Cys Asp Leu Leu Trp Ser Asp Pro Glu Asp Thr Thr Gly Trp Gly Val
195 200 205

Ser Pro Arg Gly Ala Gly Tyr Leu Phe Gly Ser Asp Val Val Ala Gln
210 215 220

Phe Asn Ala Ala Asn Asp Ile Asp Met Ile Cys Arg Ala His Gln Leu
225 230 235 240

Val Met Glu Gly Tyr Lys Trp His Phe Asn Glu Thr Val Leu Thr Val
245 250 255

Trp Ser Ala Pro Asn Tyr Cys Tyr Arg Cys Gly Asn Val Ala Ala Ile
260 265 270

Leu Glu Leu Asp Glu His Leu Gln Lys Asp Phe Ile Ile Phe Glu Ala
275 280 285

Ala Pro Gln Glu Thr Arg Gly Ile Pro Ser Lys Lys Pro Val Ala Asp
290 295 300

Tyr Phe Leu
305

<210> 42
<211> 773
<212> PRT
<213> Homo sapiens

<400> 42

Met Phe Ser Leu Ser Ser Thr Val Gln Pro Gln Val Thr Val Pro Leu
1 5 10 15

Ser His Leu Ile Asn Ala Phe His Thr Pro Lys Asn Thr Ser Val Ser
20 25 30

Leu Ser Gly Val Ser Val Ser Gln Asn Gln His Arg Asp Val Val Pro
35 40 45

Glu His Glu Ala Pro Ser Ser Glu Cys Met Phe Ser Asp Phe Leu Thr
    50   55   60

Lys Leu Asn Ile Val Ser Ile Gly Lys Gly Lys Ile Phe Glu Gly Tyr
65   70   75   80

Arg Ser Met Phe Met Glu Pro Ala Lys Arg Met Lys Lys Ser Leu Asp
                85   90   95

Thr Thr Asp Asn Trp His Ile Arg Pro Glu Pro Phe Ser Leu Ser Ile
            100   105   110

Pro Pro Ser Leu Asn Leu Arg Asp Leu Gly Leu Ser Glu Leu Lys Ile
        115   120   125

Gly Gln Ile Asp Gln Leu Val Glu Asn Leu Leu Pro Gly Phe Cys Lys
    130   135   140

Gly Lys Asn Ile Ser Ser His Trp His Thr Ser His Val Ser Ala Gln
145   150   155   160

Ser Phe Phe Glu Asn Lys Tyr Gly Asn Leu Asp Ile Phe Ser Thr Leu
                165   170   175

Arg Ser Ser Cys Leu Tyr Arg His His Ser Arg Ala Leu Gln Ser Ile
            180   185   190

Cys Ser Asp Leu Gln Tyr Trp Pro Val Phe Ile Gln Ser Arg Gly Phe
        195   200   205

Lys Thr Leu Lys Ser Arg Thr Arg Arg Leu Gln Ser Thr Ser Glu Arg
    210   215   220

Leu Ala Glu Thr Gln Asn Ile Ala Pro Ser Phe Val Lys Gly Phe Leu
225   230   235   240

Leu Arg Asp Arg Gly Ser Asp Val Glu Ser Leu Asp Lys Leu Met Lys
                245   250   255

Thr Lys Asn Ile Pro Glu Ala His Gln Asp Ala Phe Lys Thr Gly Phe
            260   265   270

Ala Glu Gly Phe Leu Lys Ala Gln Ala Leu Thr Gln Lys Thr Asn Asp
        275   280   285

Ser Leu Arg Arg Thr Arg Leu Ile Leu Phe Val Leu Leu Leu Phe Gly
    290   295   300

Ile Tyr Gly Leu Leu Lys Asn Pro Phe Leu Ser Val Arg Phe Arg Thr
305 310 315 320

Thr Thr Gly Leu Asp Ser Ala Val Asp Pro Val Gln Met Lys Asn Val
325 330 335

Thr Phe Glu His Val Lys Gly Val Glu Glu Ala Lys Gln Glu Leu Gln
340 345 350

Glu Val Val Glu Phe Leu Lys Asn Pro Gln Lys Phe Thr Ile Leu Gly
355 360 365

Gly Lys Leu Pro Lys Gly Ile Leu Leu Val Gly Pro Pro Gly Thr Gly
370 375 380

Lys Thr Leu Leu Ala Arg Ala Val Ala Gly Glu Ala Asp Val Pro Phe
385 390 395 400

Tyr Tyr Ala Ser Gly Ser Glu Phe Asp Glu Met Phe Val Gly Val Gly
405 410 415

Ala Ser Arg Ile Arg Asn Leu Phe Arg Glu Ala Lys Ala Asn Ala Pro
420 425 430

Cys Val Ile Phe Ile Asp Glu Leu Asp Ser Val Gly Gly Lys Arg Ile
435 440 445

Glu Ser Pro Met His Pro Tyr Ser Arg Gln Thr Ile Asn Gln Leu Leu
450 455 460

Ala Glu Met Asp Gly Phe Lys Pro Asn Glu Gly Val Ile Ile Ile Gly
465 470 475 480

Ala Thr Asn Phe Pro Glu Ala Leu Asp Asn Ala Leu Ile Arg Pro Gly
485 490 495

Arg Phe Asp Met Gln Val Thr Val Pro Arg Pro Asp Val Lys Gly Arg
500 505 510

Thr Glu Ile Leu Lys Trp Tyr Leu Asn Lys Ile Lys Phe Asp Gln Ser
515 520 525

Val Asp Pro Glu Ile Ile Ala Arg Gly Thr Val Gly Phe Ser Gly Ala
530 535 540

Glu Leu Glu Asn Leu Val Asn Gln Ala Ala Leu Lys Ala Ala Val Asp
545 550 555 560

Gly Lys Glu Met Val Thr Met Lys Glu Leu Glu Phe Ser Lys Asp Lys
565 570 575

Ile Leu Met Gly Pro Glu Arg Arg Ser Val Glu Ile Asp Asn Lys Asn
580 585 590

Lys Thr Ile Thr Ala Tyr His Glu Ser Gly His Ala Ile Ile Ala Tyr
595 600 605

Tyr Thr Lys Asp Ala Met Pro Ile Asn Lys Ala Thr Ile Met Pro Arg
610 615 620

Gly Pro Thr Leu Gly His Val Ser Leu Leu Pro Glu Asn Asp Arg Trp
625 630 635 640

Asn Glu Thr Arg Ala Gln Leu Leu Ala Gln Met Asp Val Ser Met Gly
645 650 655

Gly Arg Val Ala Glu Glu Leu Ile Phe Gly Thr Asp His Ile Thr Thr
660 665 670

Gly Ala Ser Ser Asp Phe Asp Asn Ala Thr Lys Ile Ala Lys Arg Met
675 680 685

Val Thr Lys Phe Gly Met Ser Glu Lys Leu Gly Val Met Thr Tyr Ser
690 695 700

Asp Thr Gly Lys Leu Ser Pro Glu Thr Gln Ser Ala Ile Glu Gln Glu
705 710 715 720

Ile Arg Ile Leu Leu Arg Asp Ser Tyr Glu Arg Ala Lys His Ile Leu
725 730 735

Lys Thr His Ala Lys Glu His Lys Asn Leu Ala Glu Ala Leu Leu Thr
740 745 750

Tyr Glu Thr Leu Asp Ala Lys Glu Ile Gln Ile Val Leu Glu Gly Lys
755 760 765

Lys Leu Glu Val Arg
770

<210> 43
<211> 534

<212> PRT
<213> Homo sapiens

<400> 43

Met Phe Ser Trp Val Ser Lys Asp Ala Arg Arg Lys Lys Glu Pro Glu
1 5 10 15

Leu Phe Gln Thr Val Ala Glu Gly Leu Arg Gln Leu Tyr Ala Gln Lys
20 25 30

Leu Leu Pro Leu Glu Glu His Tyr Arg Phe His Glu Phe His Ser Pro
35 40 45

Ala Leu Glu Asp Ala Asp Phe Asp Asn Lys Pro Met Val Leu Leu Val
50 55 60

Gly Gln Tyr Ser Thr Gly Lys Thr Thr Phe Ile Arg His Leu Ile Glu
65 70 75 80

Gln Asp Phe Pro Gly Met Arg Ile Gly Pro Glu Pro Thr Thr Asp Ser
85 90 95

Phe Ile Ala Val Met His Gly Pro Thr Glu Gly Val Val Pro Gly Asn
100 105 110

Ala Leu Val Val Asp Pro Arg Arg Pro Phe Arg Lys Leu Asn Arg Phe
115 120 125

Gly Asn Ala Phe Leu Asn Arg Phe Met Cys Ala Gln Leu Pro Asn Pro
130 135 140

Val Leu Asp Ser Ile Ser Ile Ile Asp Thr Pro Gly Ile Leu Ser Gly
145 150 155 160

Glu Lys Gln Arg Ile Ser Arg Gly Tyr Asp Phe Ala Ala Val Leu Glu
165 170 175

Trp Phe Ala Asp Cys Trp Asp Arg Ile Ile Leu Leu Phe Asp Ala His
180 185 190

Lys Gln Asp Ile Ser His Glu Phe Ser Glu Val Ile Lys Ala Leu Lys
195 200 205

Asn His Glu Asp Lys Ile Arg Met Val Leu Asn Lys Ala Asp Gln Ile
210 215 220

Glu Thr Gln Gln Leu Met Arg Val Tyr Gly Ala Leu Met Trp Ser Leu

225 230 235 240

Gly Lys Ile Ile Asn Thr Pro Glu Val Val Arg Val Tyr Ile Gly Ser
245 250 255

Phe Trp Ser His Pro Leu Leu Ile Pro Asp Asn Arg Lys Leu Phe Glu
260 265 270

Ala Glu Glu Gln Asp Leu Phe Lys Asp Ile Gln Ser Leu Pro Arg Asn
275 280 285

Ala Ala Leu Arg Lys Leu Asn Asp Leu Ile Lys Arg Ala Arg Leu Ala
290 295 300

Lys Val His Ala Tyr Ile Ile Ser Ser Leu Lys Lys Glu Met Pro Asn
305 310 315 320

Val Phe Gly Lys Glu Ser Lys Lys Lys Glu Leu Val Asn Asn Leu Gly
325 330 335

Glu Ile Tyr Gln Lys Ile Glu Arg Glu His Gln Ile Ser Pro Gly Asp
340 345 350

Phe Pro Ser Leu Arg Lys Met Gln Glu Leu Leu Gln Thr Gln Asp Phe
355 360 365

Ser Lys Phe Gln Ala Leu Lys Pro Lys Leu Leu Asp Thr Val Asp Asp
370 375 380

Met Leu Ala Asn Asp Ile Ala Arg Leu Met Val Met Val Arg Gln Glu
385 390 395 400

Glu Ser Leu Met Pro Ser Gln Val Val Lys Gly Gly Ala Phe Asp Gly
405 410 415

Thr Met Asn Gly Pro Phe Gly His Gly Tyr Gly Glu Gly Ala Gly Glu
420 425 430

Gly Ile Asp Asp Val Glu Trp Val Val Gly Lys Asp Lys Pro Ser Tyr
435 440 445

Asp Glu Ile Phe Tyr Thr Leu Ser Pro Val Asn Gly Lys Ile Thr Gly
450 455 460

Ala Asn Val Lys Lys Glu Met Val Lys Ser Lys Leu Pro Asn Thr Glu
465 470 475 480

Leu Gly Lys Ile Trp Lys Leu Ala Asp Val Asp Lys Asp Gly Leu Leu
485 490 495

Asp Asp Glu Glu Phe Ala Leu Ala Asn His Leu Ile Lys Val Lys Leu
500 505 510

Glu Gly His Glu Leu Pro Ala Asp Leu Pro Pro His Leu Val Pro Pro
515 520 525

Ser Lys Arg Arg His Glu
530

<210> 44
<211> 543
<212> PRT
<213> Homo sapiens

<400> 44

Met Phe Ser Trp Leu Lys Arg Gly Gly Ala Arg Gly Gln Gln Pro Glu
1 5 10 15

Ala Ile Arg Thr Val Thr Ser Ala Leu Lys Glu Leu Tyr Arg Thr Lys
20 25 30

Leu Leu Pro Leu Glu Glu His Tyr Arg Phe Gly Ala Phe His Ser Pro
35 40 45

Ala Leu Glu Asp Ala Asp Phe Asp Gly Lys Pro Met Val Leu Val Ala
50 55 60

Gly Gln Tyr Ser Thr Gly Lys Thr Ser Phe Ile Gln Tyr Leu Leu Glu
65 70 75 80

Gln Glu Val Pro Gly Ser Arg Val Gly Pro Glu Pro Thr Thr Asp Cys
85 90 95

Phe Val Ala Val Met His Gly Asp Thr Glu Gly Thr Val Pro Gly Asn
100 105 110

Ala Leu Val Val Asp Pro Asp Lys Pro Phe Arg Lys Leu Asn Pro Phe
115 120 125

Gly Asn Thr Phe Leu Asn Arg Phe Met Cys Ala Gln Leu Pro Asn Gln
130 135 140

Val Leu Glu Ser Ile Ser Ile Ile Asp Thr Pro Gly Ile Leu Ser Gly
145 150 155 160

Ala Lys Gln Arg Val Ser Arg Gly Tyr Asp Phe Pro Ala Val Leu Arg
165 170 175

Trp Phe Ala Glu Arg Val Asp Leu Ile Ile Leu Leu Phe Asp Ala His
180 185 190

Lys Leu Glu Ile Ser Asp Glu Phe Ser Glu Ala Ile Gly Ala Leu Arg
195 200 205

Gly His Glu Asp Lys Ile Arg Val Val Leu Asn Lys Ala Asp Met Val
210 215 220

Glu Thr Gln Gln Leu Met Arg Val Tyr Gly Ala Leu Met Trp Ala Leu
225 230 235 240

Gly Lys Val Val Gly Thr Pro Glu Val Leu Arg Val Tyr Ile Gly Ser
245 250 255

Phe Trp Ser Gln Pro Leu Leu Val Pro Asp Asn Arg Arg Leu Phe Glu
260 265 270

Leu Glu Glu Gln Asp Leu Phe Arg Asp Ile Gln Gly Leu Pro Arg His
275 280 285

Ala Ala Leu Arg Lys Leu Asn Asp Leu Val Lys Arg Ala Arg Leu Val
290 295 300

Arg Val His Ala Tyr Ile Ile Ser Tyr Leu Lys Lys Glu Met Pro Ser
305 310 315 320

Val Phe Gly Lys Glu Asn Lys Lys Lys Gln Leu Ile Leu Lys Leu Pro
325 330 335

Val Ile Phe Ala Lys Ile Gln Leu Glu His His Ile Ser Pro Gly Asp
340 345 350

Phe Pro Asp Cys Gln Lys Met Gln Glu Leu Leu Met Ala His Asp Phe
355 360 365

Thr Lys Phe His Ser Leu Lys Pro Lys Leu Leu Glu Ala Leu Asp Glu
370 375 380

Met Leu Thr His Asp Ile Ala Lys Leu Met Pro Leu Leu Arg Gln Glu
385 390 395 400

Glu Leu Glu Ser Thr Glu Val Gly Val Gln Gly Gly Ala Phe Glu Gly
405 410 415

Thr His Met Gly Pro Phe Val Glu Arg Gly Pro Asp Glu Ala Met Glu
420 425 430

Asp Gly Glu Glu Gly Ser Asp Asp Glu Ala Glu Trp Val Val Thr Lys
435 440 445

Asp Lys Ser Lys Tyr Asp Glu Ile Phe Tyr Asn Leu Ala Pro Ala Asp
450 455 460

Gly Lys Leu Ser Gly Ser Lys Ala Lys Thr Trp Met Val Gly Thr Lys
465 470 475 480

Leu Pro Asn Ser Val Leu Gly Arg Ile Trp Lys Leu Ser Asp Val Asp
485 490 495

Arg Asp Gly Met Leu Asp Asp Glu Glu Phe Ala Leu Ala Ser His Leu
500 505 510

Ile Glu Ala Lys Leu Glu Gly His Gly Leu Pro Ala Asn Leu Pro Arg
515 520 525

Arg Leu Val Pro Pro Ser Lys Arg Arg His Lys Gly Ser Ala Glu
530 535 540

<210> 45
<211> 535
<212> PRT
<213> Homo sapiens

<400> 45

Met Phe Ser Trp Leu Gly Thr Asp Asp Arg Arg Arg Lys Asp Pro Glu
1 5 10 15

Val Phe Gln Thr Val Ser Glu Gly Leu Lys Lys Leu Tyr Lys Ser Lys
20 25 30

Leu Leu Pro Leu Glu Glu His Tyr Arg Phe His Glu Phe His Ser Pro
35 40 45

Ala Leu Glu Asp Ala Asp Phe Asp Asn Lys Pro Met Val Leu Leu Val
50 55 60

Gly Gln Tyr Ser Thr Gly Lys Thr Thr Phe Ile Arg Tyr Leu Leu Glu
65 70 75 80

Gln Asp Phe Pro Gly Met Arg Ile Gly Pro Glu Pro Thr Thr Asp Ser
85 90 95

Phe Ile Ala Val Met Gln Gly Asp Met Glu Gly Ile Ile Pro Gly Asn
100 105 110

Ala Leu Val Val Asp Pro Lys Lys Pro Phe Arg Lys Leu Asn Ala Phe
115 120 125

Gly Asn Ala Phe Leu Asn Arg Phe Val Cys Ala Gln Leu Pro Asn Pro
130 135 140

Val Leu Glu Ser Ile Ser Val Ile Asp Thr Pro Gly Ile Leu Ser Gly
145 150 155 160

Glu Lys Gln Arg Ile Ser Arg Gly Tyr Asp Phe Ala Ala Val Leu Glu
165 170 175

Trp Phe Ala Glu Arg Val Asp Arg Ile Ile Leu Leu Phe Asp Ala His
180 185 190

Lys Leu Asp Ile Ser Asp Glu Phe Ser Glu Val Ile Lys Ala Leu Lys
195 200 205

Asn His Glu Asp Lys Met Arg Val Val Leu Asn Lys Ala Asp Gln Ile
210 215 220

Glu Thr Gln Gln Leu Met Arg Val Tyr Gly Ala Leu Met Trp Ser Leu
225 230 235 240

Gly Lys Ile Val Asn Thr Pro Glu Val Ile Arg Val Tyr Ile Gly Ser
245 250 255

Phe Trp Ser His Pro Leu Leu Ile Pro Asp Asn Arg Lys Leu Phe Glu
260 265 270

Ala Glu Glu Gln Asp Leu Phe Arg Asp Ile Gln Ser Leu Pro Arg Asn
275 280 285

Ala Ala Leu Arg Lys Leu Asn Asp Leu Ile Lys Arg Ala Arg Leu Ala
290 295 300

Lys Val His Ala Tyr Ile Ile Ser Ser Leu Lys Lys Glu Met Pro Ser
305 310 315 320

Val Phe Gly Lys Asp Asn Lys Lys Lys Glu Leu Val Asn Asn Leu Ala

325 330 335

Glu Ile Tyr Gly Arg Ile Glu Arg Glu His Gln Ile Ser Pro Gly Asp
340 345 350

Phe Pro Asn Leu Lys Arg Met Gln Asp Gln Leu Gln Ala Gln Asp Phe
355 360 365

Ser Lys Phe Gln Pro Leu Lys Ser Lys Leu Leu Glu Val Val Asp Asp
370 375 380

Met Leu Ala His Asp Ile Ala Gln Leu Met Val Leu Val Arg Gln Glu
385 390 395 400

Glu Ser Gln Arg Pro Ile Gln Met Val Lys Gly Gly Ala Phe Glu Gly
405 410 415

Thr Leu His Gly Pro Phe Gly His Gly Tyr Gly Glu Gly Ala Gly Glu
420 425 430

Gly Ile Asp Asp Ala Glu Trp Val Val Ala Arg Asp Lys Pro Met Tyr
435 440 445

Asp Glu Ile Phe Tyr Thr Leu Ser Pro Val Asp Gly Lys Ile Thr Gly
450 455 460

Ala Asn Ala Lys Lys Glu Met Val Arg Ser Lys Leu Pro Asn Ser Val
465 470 475 480

Leu Gly Lys Ile Trp Lys Leu Ala Asp Ile Asp Lys Asp Gly Met Leu
485 490 495

Asp Asp Asp Glu Phe Ala Leu Ala Asn His Leu Ile Lys Val Lys Leu
500 505 510

Glu Gly His Glu Leu Pro Asn Glu Leu Pro Ala His Leu Leu Pro Pro
515 520 525

Ser Lys Arg Lys Val Ala Glu
530 535

<210> 46
<211> 541
<212> PRT
<213> Homo sapiens

<400> 46

Met Phe Ser Trp Met Gly Arg Gln Ala Gly Gly Arg Glu Arg Ala Gly
1 5 10 15

Gly Ala Asp Ala Val Gln Thr Val Thr Gly Gly Leu Arg Ser Leu Tyr
20 25 30

Leu Arg Lys Val Leu Pro Leu Glu Glu Ala Tyr Arg Phe His Glu Phe
35 40 45

His Ser Pro Ala Leu Glu Asp Ala Asp Phe Glu Asn Lys Pro Met Ile
50 55 60

Leu Leu Val Gly Gln Tyr Ser Thr Gly Lys Thr Thr Phe Ile Arg Tyr
65 70 75 80

Leu Leu Glu Gln Asp Phe Pro Gly Met Arg Ile Gly Pro Glu Pro Thr
85 90 95

Thr Asp Ser Phe Ile Ala Val Met Tyr Gly Glu Thr Glu Gly Ser Thr
100 105 110

Pro Gly Asn Ala Leu Val Val Asp Pro Lys Lys Pro Phe Arg Lys Leu
115 120 125

Ser Arg Phe Gly Asn Ala Phe Leu Asn Arg Phe Met Cys Ser Gln Leu
130 135 140

Pro Asn Gln Val Leu Lys Ser Ile Ser Val Ile Asp Ser Pro Gly Ile
145 150 155 160

Leu Ser Gly Glu Lys Gln Arg Ile Ser Arg Gly Tyr Asp Phe Cys Gln
165 170 175

Val Leu Gln Trp Phe Ala Glu Arg Val Asp Arg Ile Ile Leu Leu Phe
180 185 190

Asp Ala His Lys Leu Asp Ile Ser Asp Glu Phe Ser Glu Ala Ile Lys
195 200 205

Ala Phe Arg Gly Gln Asp Asp Lys Ile Arg Val Val Leu Asn Lys Ala
210 215 220

Asp Gln Val Asp Thr Gln Gln Leu Met Arg Val Tyr Gly Ala Leu Met
225 230 235 240

Trp Ser Leu Gly Lys Val Ile Asn Thr Pro Glu Val Leu Arg Val Tyr
245 250 255

Ile Gly Ser Phe Trp Ala Gln Pro Leu Gln Asn Thr Asp Asn Arg Arg
260 265 270

Leu Phe Glu Ala Glu Ala Gln Asp Leu Phe Arg Asp Ile Gln Ser Leu
275 280 285

Pro Gln Lys Ala Ala Val Arg Lys Leu Asn Asp Leu Ile Lys Arg Ala
290 295 300

Arg Leu Ala Lys Val His Ala Tyr Ile Ile Ser Tyr Leu Lys Lys Glu
305 310 315 320

Met Pro Ser Val Phe Gly Lys Glu Asn Lys Lys Arg Glu Leu Ile Ser
325 330 335

Arg Leu Pro Glu Ile Tyr Ile Gln Leu Gln Arg Glu Tyr Gln Ile Ser
340 345 350

Ala Gly Asp Phe Pro Glu Val Lys Ala Met Gln Glu Gln Leu Glu Asn
355 360 365

Tyr Asp Phe Thr Lys Phe His Ser Leu Lys Pro Lys Leu Ile Glu Ala
370 375 380

Val Asp Asn Met Leu Ser Asn Lys Ile Ser Pro Leu Met Asn Leu Ile
385 390 395 400

Ser Gln Glu Glu Thr Ser Thr Pro Thr Gln Leu Val Gln Gly Gly Ala
405 410 415

Phe Asp Gly Thr Thr Glu Gly Pro Phe Asn Gln Gly Tyr Gly Glu Gly
420 425 430

Ala Lys Glu Gly Ala Asp Glu Glu Glu Trp Val Val Ala Lys Asp Lys
435 440 445

Pro Val Tyr Asp Glu Leu Phe Tyr Thr Leu Ser Pro Ile Asn Gly Lys
450 455 460

Ile Ser Gly Val Asn Ala Lys Lys Glu Met Val Thr Ser Lys Leu Pro
465 470 475 480

Asn Ser Val Leu Gly Lys Ile Trp Lys Leu Ala Asp Cys Asp Cys Asp
485 490 495

Gly Met Leu Asp Glu Glu Glu Phe Ala Leu Ala Lys His Leu Ile Lys
500 505 510

Ile Lys Leu Asp Gly Tyr Glu Leu Pro Ser Ser Leu Pro Pro His Leu
515 520 525

Val Pro Pro Ser His Arg Lys Ser Leu Pro Lys Ala Asp
530 535 540

<210> 47
<211> 1366
<212> PRT
<213> Homo sapiens

<400> 47

Met Leu Ala Val Gly Pro Ala Met Asp Arg Asp Tyr Pro Gln His Glu
1 5 10 15

Pro Pro Pro Ala Gly Ser Leu Leu Tyr Ser Pro Pro Pro Leu Gln Ser
20 25 30

Ala Met Leu His Cys Pro Tyr Trp Asn Thr Phe Ser Leu Pro Pro Tyr
35 40 45

Pro Ala Phe Ser Ser Asp Ser Arg Pro Phe Met Ser Ser Ala Ser Phe
50 55 60

Leu Gly Ser Gln Pro Cys Pro Asp Thr Ser Tyr Ala Pro Val Ala Thr
65 70 75 80

Ala Ser Ser Leu Pro Pro Lys Thr Cys Asp Phe Ala Gln Asp Ser Ser
85 90 95

Tyr Phe Glu Asp Phe Ser Asn Ile Ser Ile Phe Ser Ser Ser Val Asp
100 105 110

Ser Leu Ser Asp Ile Val Asp Thr Pro Asp Phe Leu Pro Ala Asp Ser
115 120 125

Leu Asn Gln Val Ser Thr Ile Trp Asp Asp Asn Pro Ala Pro Ser Thr
130 135 140

His Asp Lys Leu Phe Gln Leu Ser Arg Pro Phe Ala Gly Phe Glu Asp
145 150 155 160

Phe Leu Pro Ser His Ser Thr Pro Leu Leu Val Ser Tyr Gln Glu Gln
165 170 175

Ser Val Gln Ser Gln Pro Glu Glu Glu Asp Glu Ala Glu Glu Glu Glu
180 185 190

Ala Glu Glu Leu Gly His Thr Glu Thr Tyr Ala Asp Tyr Val Pro Ser
195 200 205

Lys Ser Lys Ile Gly Lys Gln His Pro Asp Arg Val Val Glu Thr Ser
210 215 220

Thr Leu Ser Ser Val Pro Pro Pro Asp Ile Thr Tyr Thr Leu Ala Leu
225 230 235 240

Pro Ser Asp Ser Gly Ala Leu Ser Ala Leu Gln Leu Glu Ala Ile Thr
245 250 255

Tyr Ala Cys Gln Gln His Glu Val Leu Leu Pro Ser Gly Gln Arg Ala
260 265 270

Gly Phe Leu Ile Gly Asp Gly Ala Gly Val Gly Lys Gly Arg Thr Val
275 280 285

Ala Gly Val Ile Leu Glu Asn His Leu Arg Gly Arg Lys Lys Ala Leu
290 295 300

Trp Phe Ser Val Ser Asn Asp Leu Lys Tyr Asp Ala Glu Arg Asp Leu
305 310 315 320

Arg Asp Ile Glu Ala Thr Gly Ile Ala Val His Ala Leu Ser Lys Ile
325 330 335

Lys Tyr Gly Asp Thr Thr Thr Ser Glu Gly Val Leu Phe Ala Thr Tyr
340 345 350

Ser Ala Leu Ile Gly Glu Ser Gln Ala Gly Gly Gln His Arg Thr Arg
355 360 365

Leu Arg Gln Ile Leu Asp Trp Cys Gly Glu Ala Phe Glu Gly Val Ile
370 375 380

Val Phe Asp Glu Cys His Lys Ala Lys Asn Ala Gly Ser Thr Lys Met
385 390 395 400

Gly Lys Ala Val Leu Asp Leu Gln Asn Lys Leu Pro Leu Ala Arg Val
405 410 415

Val Tyr Ala Ser Ala Thr Gly Ala Ser Glu Pro Arg Asn Met Ile Tyr

420 425 430

Met Ser Arg Leu Gly Ile Trp Gly Glu Gly Thr Pro Phe Arg Asn Phe
435 440 445

Glu Glu Phe Leu His Ala Ile Glu Lys Arg Gly Val Gly Ala Met Glu
450 455 460

Ile Val Ala Met Asp Met Lys Val Ser Gly Met Tyr Ile Ala Arg Gln
465 470 475 480

Leu Ser Phe Ser Gly Val Thr Phe Arg Ile Glu Glu Ile Pro Leu Ala
485 490 495

Pro Ala Phe Glu Cys Val Tyr Asn Arg Ala Ala Leu Leu Trp Ala Glu
500 505 510

Ala Leu Asn Val Phe Gln Gln Ala Ala Asp Trp Ile Gly Leu Glu Ser
515 520 525

Arg Lys Ser Leu Trp Gly Gln Phe Trp Ser Ala His Gln Arg Phe Phe
530 535 540

Lys Tyr Leu Cys Ile Ala Ala Lys Val Arg Arg Leu Val Glu Leu Ala
545 550 555 560

Arg Glu Glu Leu Ala Arg Asp Lys Cys Val Val Ile Gly Leu Gln Ser
565 570 575

Thr Gly Glu Ala Arg Thr Arg Glu Val Leu Gly Glu Asn Asp Gly His
580 585 590

Leu Asn Cys Phe Val Ser Ala Ala Glu Gly Val Phe Leu Ser Leu Ile
595 600 605

Gln Lys His Phe Pro Ser Thr Lys Arg Lys Arg Asp Arg Gly Ala Gly
610 615 620

Ser Lys Arg Lys Arg Arg Pro Arg Gly Arg Gly Ala Lys Ala Pro Arg
625 630 635 640

Leu Ala Cys Glu Thr Ala Gly Val Ile Arg Ile Ser Asp Asp Ser Ser
645 650 655

Thr Glu Ser Asp Pro Gly Leu Asp Ser Asp Phe Asn Ser Ser Pro Glu
660 665 670

Ser Leu Val Asp Asp Asp Val Val Ile Val Asp Ala Val Gly Leu Pro
675 680 685

Ser Asp Asp Arg Gly Ser Leu Cys Leu Leu Gln Arg Asp Pro His Gly
690 695 700

Pro Gly Val Leu Glu Arg Val Glu Arg Leu Lys Gln Asp Leu Leu Asp
705 710 715 720

Lys Val Arg Arg Leu Gly Arg Glu Leu Pro Val Asn Thr Leu Asp Glu
725 730 735

Leu Ile Asp Gln Leu Gly Gly Pro Gln Arg Val Ala Glu Met Thr Gly
740 745 750

Arg Lys Gly Arg Val Val Ser Arg Pro Asp Gly Thr Val Ala Phe Glu
755 760 765

Ser Arg Ala Glu Gln Gly Leu Ser Ile Asp His Val Asn Leu Arg Glu
770 775 780

Lys Gln Arg Phe Met Ser Gly Glu Lys Leu Val Ala Ile Ile Ser Glu
785 790 795 800

Ala Ser Ser Ser Gly Val Ser Leu Gln Ala Asp Arg Arg Val Gln Asn
805 810 815

Gln Arg Arg Arg Val His Met Thr Leu Glu Leu Pro Trp Ser Ala Asp
820 825 830

Arg Ala Ile Gln Gln Phe Gly Arg Thr His Arg Ser Asn Gln Val Ser
835 840 845

Ala Pro Glu Tyr Val Phe Leu Ile Ser Glu Leu Ala Gly Glu Arg Arg
850 855 860

Phe Ala Ser Ile Val Ala Lys Arg Leu Glu Ser Leu Gly Ala Leu Thr
865 870 875 880

His Gly Asp Arg Arg Ala Thr Glu Ser Arg Asp Leu Ser Lys Tyr Asn
885 890 895

Phe Glu Asn Lys Tyr Gly Thr Arg Ala Leu His Cys Val Leu Thr Thr
900 905 910

Ile Leu Ser Gln Thr Glu Asn Lys Val Pro Val Pro Gln Gly Tyr Pro

915 920 925

Gly Gly Val Pro Thr Phe Phe Arg Asp Met Lys Gln Gly Leu Leu Ser
930 935 940

Val Gly Ile Gly Gly Arg Glu Ser Arg Asn Gly Cys Leu Asp Val Glu
945 950 955 960

Lys Asp Cys Ser Ile Thr Lys Phe Leu Asn Arg Ile Leu Gly Leu Glu
965 970 975

Val His Lys Gln Asn Ala Leu Phe Gln Tyr Phe Ser Asp Thr Phe Asp
980 985 990

His Leu Ile Glu Met Asp Lys Arg Glu Gly Lys Tyr Asp Met Gly Ile
995 1000 1005

Leu Asp Leu Ala Pro Gly Ile Glu Glu Ile Tyr Glu Glu Ser Gln
1010 1015 1020

Gln Val Phe Leu Ala Pro Gly His Pro Gln Asp Gly Gln Val Val
1025 1030 1035

Phe Tyr Lys Ile Ser Val Asp Arg Gly Leu Lys Trp Glu Asp Ala
1040 1045 1050

Phe Ala Lys Ser Leu Ala Leu Thr Gly Pro Tyr Asp Gly Phe Tyr
1055 1060 1065

Leu Ser Tyr Lys Val Arg Gly Asn Lys Pro Ser Cys Leu Leu Ala
1070 1075 1080

Glu Gln Asn Arg Gly Gln Phe Phe Thr Val Tyr Lys Pro Asn Ile
1085 1090 1095

Gly Arg Gln Ser Gln Leu Glu Ala Leu Asp Ser Leu Arg Arg Lys
1100 1105 1110

Phe His Arg Val Thr Ala Glu Glu Ala Lys Glu Pro Trp Glu Ser
1115 1120 1125

Gly Tyr Ala Leu Ser Leu Thr His Cys Ser His Ser Ala Trp Asn
1130 1135 1140

Arg His Cys Arg Leu Ala Gln Glu Gly Lys Asp Cys Leu Gln Gly
1145 1150 1155

Leu Arg Leu Arg His His Tyr Met Leu Cys Gly Ala Leu Leu Arg
1160 1165 1170

Val Trp Gly Arg Ile Ala Ala Val Met Ala Asp Val Ser Ser Ser
1175 1180 1185

Ser Tyr Leu Gln Ile Val Arg Leu Lys Thr Lys Asp Arg Lys Lys
1190 1195 1200

Gln Val Gly Ile Lys Ile Pro Glu Gly Cys Val Arg Arg Val Leu
1205 1210 1215

Gln Glu Leu Arg Leu Met Asp Ala Asp Val Lys Arg Arg Gln Ala
1220 1225 1230

Pro Ala Leu Gly Cys Pro Ala Pro Pro Ala Pro Arg Pro Leu Ala
1235 1240 1245

Leu Pro Cys Gly Pro Gly Glu Val Leu Asp Leu Thr Tyr Ser Pro
1250 1255 1260

Pro Ala Glu Ala Phe Pro Pro Pro Pro His Phe Ser Phe Pro Ala
1265 1270 1275

Pro Leu Ser Leu Asp Ala Gly Pro Gly Val Val Pro Leu Gly Thr
1280 1285 1290

Pro Asp Ala Gln Ala Asp Pro Ala Ala Leu Ala His Gln Gly Cys
1295 1300 1305

Asp Ile Asn Phe Lys Glu Val Leu Glu Asp Met Leu Arg Ser Leu
1310 1315 1320

His Ala Gly Pro Pro Ser Glu Gly Ala Leu Gly Glu Gly Ala Gly
1325 1330 1335

Ala Gly Gly Ala Ala Gly Gly Gly Pro Glu Arg Gln Ser Val Ile
1340 1345 1350

Gln Phe Ser Pro Pro Phe Pro Gly Ala Gln Ala Pro Leu
1355 1360 1365

<210> 48
<211> 1392
<212> PRT
<213> Homo sapiens

<400> 48

Met Val Glu Pro Gly Gln Asp Leu Leu Leu Ala Ala Leu Ser Glu Ser
1   5   10   15

Gly Ile Ser Pro Asn Asp Leu Phe Asp Ile Asp Gly Gly Asp Ala Gly
            20   25   30

Leu Ala Thr Pro Met Pro Thr Pro Ser Val Gln Gln Ser Val Pro Leu
        35   40   45

Ser Ala Leu Glu Leu Gly Leu Glu Thr Glu Ala Ala Val Pro Val Lys
    50   55   60

Gln Glu Pro Glu Thr Val Pro Thr Pro Ala Leu Leu Asn Val Arg Gln
65   70   75   80

Pro Pro Ser Thr Thr Thr Phe Val Leu Asn Gln Ile Asn His Leu Pro
                85   90   95

Pro Leu Gly Ser Thr Ile Val Met Thr Lys Thr Pro Pro Val Thr Thr
            100   105   110

Asn Arg Gln Thr Ile Thr Leu Thr Lys Phe Ile Gln Thr Thr Ala Ser
        115   120   125

Thr Arg Pro Ser Val Ser Ala Pro Thr Val Arg Asn Ala Met Thr Ser
    130   135   140

Ala Pro Ser Lys Asp Gln Val Gln Leu Lys Asp Leu Leu Lys Asn Asn
145   150   155   160

Ser Leu Asn Glu Leu Met Lys Leu Lys Pro Pro Ala Asn Ile Ala Gln
                165   170   175

Pro Val Ala Thr Ala Ala Thr Asp Val Ser Asn Gly Thr Val Lys Lys
            180   185   190

Glu Ser Ser Asn Lys Glu Gly Ala Arg Met Trp Ile Asn Asp Met Lys
        195   200   205

Met Arg Ser Phe Ser Pro Thr Met Lys Val Pro Val Val Lys Glu Asp
    210   215   220

Asp Glu Pro Glu Glu Glu Asp Glu Glu Glu Met Gly His Ala Glu Thr
225   230   235   240

Tyr Ala Glu Tyr Met Pro Ile Lys Leu Lys Ile Gly Leu Arg His Pro
245 250 255

Asp Ala Val Val Glu Thr Ser Ser Leu Ser Ser Val Thr Pro Pro Asp
260 265 270

Val Trp Tyr Lys Thr Ser Ile Ser Glu Glu Thr Ile Asp Asn Gly Trp
275 280 285

Leu Ser Ala Leu Gln Leu Glu Ala Ile Thr Tyr Ala Ala Gln Gln His
290 295 300

Glu Thr Phe Leu Pro Asn Gly Asp Arg Ala Gly Phe Leu Ile Gly Asp
305 310 315 320

Gly Ala Gly Val Gly Lys Gly Arg Thr Ile Ala Gly Ile Ile Tyr Glu
325 330 335

Asn Tyr Leu Leu Ser Arg Lys Arg Ala Leu Trp Phe Ser Val Ser Asn
340 345 350

Asp Leu Lys Tyr Asp Ala Glu Arg Asp Leu Arg Asp Ile Gly Ala Lys
355 360 365

Asn Ile Leu Val His Ser Leu Asn Lys Phe Lys Tyr Gly Lys Ile Ser
370 375 380

Ser Lys His Asn Gly Ser Val Lys Lys Gly Val Ile Phe Ala Thr Tyr
385 390 395 400

Ser Ser Leu Ile Gly Glu Ser Gln Ser Gly Gly Lys Tyr Lys Thr Arg
405 410 415

Leu Lys Gln Leu Leu His Trp Cys Gly Asp Asp Phe Asp Gly Val Ile
420 425 430

Val Phe Asp Glu Cys His Lys Ala Lys Asn Leu Cys Pro Val Gly Ser
435 440 445

Ser Lys Pro Thr Lys Thr Gly Leu Ala Val Leu Glu Leu Gln Asn Lys
450 455 460

Leu Pro Lys Ala Arg Val Val Tyr Ala Ser Ala Thr Gly Ala Ser Glu
465 470 475 480

Pro Arg Asn Met Ala Tyr Met Asn Arg Leu Gly Ile Trp Gly Glu Gly
485 490 495

Thr Pro Phe Arg Glu Phe Ser Asp Phe Ile Gln Ala Val Glu Arg Arg
500 505 510

Gly Val Gly Ala Met Glu Ile Val Ala Met Asp Met Lys Leu Arg Gly
515 520 525

Met Tyr Ile Ala Arg Gln Leu Ser Phe Thr Gly Val Thr Phe Lys Ile
530 535 540

Glu Glu Val Leu Leu Ser Gln Ser Tyr Val Lys Met Tyr Asn Lys Ala
545 550 555 560

Val Lys Leu Trp Val Ile Ala Arg Glu Arg Phe Gln Gln Ala Ala Asp
565 570 575

Leu Ile Asp Ala Glu Gln Arg Met Lys Lys Ser Met Trp Gly Gln Phe
580 585 590

Trp Ser Ala His Gln Arg Phe Phe Lys Tyr Leu Cys Ile Ala Ser Lys
595 600 605

Val Lys Arg Val Val Gln Leu Ala Arg Glu Glu Ile Lys Asn Gly Lys
610 615 620

Cys Val Val Ile Gly Leu Gln Ser Thr Gly Glu Ala Arg Thr Leu Glu
625 630 635 640

Ala Leu Glu Glu Gly Gly Gly Glu Leu Asn Asp Phe Val Ser Thr Ala
645 650 655

Lys Gly Val Leu Gln Ser Leu Ile Glu Lys His Phe Pro Ala Pro Asp
660 665 670

Arg Lys Lys Leu Tyr Ser Leu Leu Gly Ile Asp Leu Thr Ala Pro Ser
675 680 685

Asn Asn Ser Ser Pro Arg Asp Ser Pro Cys Lys Glu Asn Lys Ile Lys
690 695 700

Lys Arg Lys Gly Glu Glu Ile Thr Arg Glu Ala Lys Lys Ala Arg Lys
705 710 715 720

Val Gly Gly Leu Thr Gly Ser Ser Ser Asp Asp Ser Gly Ser Glu Ser
725 730 735

Asp Ala Ser Asp Asn Glu Glu Ser Asp Tyr Glu Ser Ser Lys Asn Met
740 745 750

Ser Ser Gly Asp Asp Asp Asp Phe Asn Pro Phe Leu Asp Glu Ser Asn
755 760 765

Glu Asp Asp Glu Ser Asp Pro Trp Leu Ile Arg Lys Asp His Lys Lys
770 775 780

Asn Lys Glu Lys Lys Lys Lys Lys Ser Ile Asp Pro Asp Ser Ile Gln
785 790 795 800

Ser Ala Leu Leu Ala Ser Gly Leu Gly Ser Lys Arg Pro Ser Phe Ser
805 810 815

Ser Thr Pro Val Ile Ser Pro Ala Pro Asn Ser Thr Pro Ala Asn Ser
820 825 830

Asn Thr Asn Ser Asn Ser Ser Leu Ile Thr Ser Gln Asp Ala Val Glu
835 840 845

Arg Ala Gln Gln Met Lys Lys Asp Leu Leu Asp Lys Leu Glu Lys Leu
850 855 860

Ala Glu Asp Leu Pro Pro Asn Thr Leu Asp Glu Leu Ile Asp Glu Leu
865 870 875 880

Gly Gly Pro Glu Asn Val Ala Glu Met Thr Gly Arg Lys Gly Arg Val
885 890 895

Val Ser Asn Asp Asp Gly Ser Ile Ser Tyr Glu Ser Arg Ser Glu Leu
900 905 910

Asp Val Pro Val Glu Ile Leu Asn Ile Thr Glu Lys Gln Arg Phe Met
915 920 925

Asp Gly Asp Lys Asn Ile Ala Ile Ile Ser Glu Ala Ala Ser Ser Gly
930 935 940

Ile Ser Leu Gln Ala Asp Arg Arg Ala Lys Asn Gln Arg Arg Arg Val
945 950 955 960

His Met Thr Leu Glu Leu Pro Trp Ser Ala Asp Arg Ala Ile Gln Gln
965 970 975

Phe Gly Arg Thr His Arg Ser Asn Gln Val Thr Ala Pro Glu Tyr Val
980 985 990

Phe Leu Ile Ser Glu Leu Ala Gly Glu Gln Arg Phe Ala Ser Ile Val
995 1000 1005

Ala Lys Arg Leu Glu Ser Leu Gly Ala Leu Thr His Gly Asp Arg
1010 1015 1020

Arg Ala Thr Glu Ser Arg Asp Leu Ser Arg Phe Asn Phe Asp Asn
1025 1030 1035

Lys Tyr Gly Arg Asn Ala Leu Glu Ile Val Met Lys Ser Ile Val
1040 1045 1050

Asn Leu Asp Ser Pro Met Val Ser Pro Pro Pro Asp Tyr Pro Gly
1055 1060 1065

Glu Phe Phe Lys Asp Val Arg Gln Gly Leu Ile Gly Val Gly Leu
1070 1075 1080

Ile Asn Val Glu Asp Arg Ser Gly Ile Leu Thr Leu Asp Lys Asp
1085 1090 1095

Tyr Asn Asn Ile Gly Lys Phe Leu Asn Arg Ile Leu Gly Met Glu
1100 1105 1110

Val His Gln Gln Asn Ala Leu Phe Gln Tyr Phe Ala Asp Thr Leu
1115 1120 1125

Thr Ala Val Val Gln Asn Ala Lys Lys Asn Gly Arg Tyr Asp Met
1130 1135 1140

Gly Ile Leu Asp Leu Gly Ser Gly Asp Glu Lys Val Arg Lys Ser
1145 1150 1155

Asp Val Lys Lys Phe Leu Thr Pro Gly Tyr Ser Thr Ser Gly His
1160 1165 1170

Val Glu Leu Tyr Thr Ile Ser Val Glu Arg Gly Met Ser Trp Glu
1175 1180 1185

Glu Ala Thr Lys Ile Trp Ala Glu Leu Thr Gly Pro Asp Asp Gly
1190 1195 1200

Phe Tyr Leu Ser Leu Gln Ile Arg Asn Asn Lys Lys Thr Ala Ile
1205 1210 1215

Leu Val Lys Glu Val Asn Pro Lys Lys Lys Leu Phe Leu Val Tyr
1220 1225 1230

Arg Pro Asn Thr Gly Lys Gln Leu Lys Leu Glu Ile Tyr Ala Asp
1235 1240 1245

Leu Lys Lys Lys Tyr Lys Lys Val Val Ser Asp Asp Ala Leu Met
1250 1255 1260

His Trp Leu Asp Gln Tyr Asn Ser Ser Ala Asp Thr Cys Thr His
1265 1270 1275

Ala Tyr Trp Arg Gly Asn Cys Lys Lys Ala Ser Leu Gly Leu Val
1280 1285 1290

Cys Glu Ile Gly Leu Arg Cys Arg Thr Tyr Tyr Val Leu Cys Gly
1295 1300 1305

Ser Val Leu Ser Val Trp Thr Lys Val Glu Gly Val Leu Ala Ser
1310 1315 1320

Val Ser Gly Thr Asn Val Lys Met Gln Ile Val Arg Leu Arg Thr
1325 1330 1335

Glu Asp Gly Gln Arg Ile Val Gly Leu Ile Ile Pro Ala Asn Cys
1340 1345 1350

Val Ser Pro Leu Val Asn Leu Leu Ser Thr Ser Asp Gln Ser Gln
1355 1360 1365

Gln Leu Ala Val Gln Gln Lys Gln Leu Trp Gln Gln His His Pro
1370 1375 1380

Gln Ser Ile Thr Asn Leu Ser Asn Ala
1385 1390

<210> 49
<211> 1327
<212> PRT
<213> Homo sapiens

<400> 49

Met Ala Ala Ser Arg Arg Ser Gln His His His His His His Gln Gln
1 5 10 15

Gln Leu Gln Pro Ala Pro Gly Ala Ser Ala Pro Pro Pro Pro Pro Pro
20 25 30

Pro Pro Leu Ser Pro Gly Leu Ala Pro Gly Thr Thr Pro Ala Ser Pro
35 40 45

Thr Ala Ser Gly Leu Ala Pro Phe Ala Ser Pro Arg His Gly Leu Ala
50 55 60

Leu Pro Glu Gly Asp Gly Ser Arg Asp Pro Pro Asp Arg Pro Arg Ser
65 70 75 80

Pro Asp Pro Val Asp Gly Thr Ser Cys Cys Ser Thr Thr Ser Thr Ile
85 90 95

Cys Thr Val Ala Ala Ala Pro Val Val Pro Ala Val Ser Thr Ser Ser
100 105 110

Ala Ala Gly Val Ala Pro Asn Pro Ala Gly Ser Gly Ser Asn Asn Ser
115 120 125

Pro Ser Ser Ser Ser Ser Pro Thr Ser Ser Ser Ser Ser Ser Pro Ser
130 135 140

Ser Pro Gly Ser Ser Leu Ala Glu Ser Pro Glu Ala Ala Gly Val Ser
145 150 155 160

Ser Thr Ala Pro Leu Gly Pro Gly Ala Ala Gly Pro Gly Thr Gly Val
165 170 175

Pro Ala Val Ser Gly Ala Leu Arg Glu Leu Leu Glu Ala Cys Arg Asn
180 185 190

Gly Asp Val Ser Arg Val Lys Arg Leu Val Asp Ala Ala Asn Val Asn
195 200 205

Ala Lys Asp Met Ala Gly Arg Lys Ser Ser Pro Leu His Phe Ala Ala
210 215 220

Gly Phe Gly Arg Lys Asp Val Val Glu His Leu Leu Gln Met Gly Ala
225 230 235 240

Asn Val His Ala Arg Asp Asp Gly Gly Leu Ile Pro Leu His Asn Ala
245 250 255

Cys Ser Phe Gly His Ala Glu Val Val Ser Leu Leu Leu Cys Gln Gly
260 265 270

Ala Asp Pro Asn Ala Arg Asp Asn Trp Asn Tyr Thr Pro Leu His Glu

275 280 285

Ala Ala Ile Lys Gly Lys Ile Asp Val Cys Ile Val Leu Leu Gln His
290 295 300

Gly Ala Asp Pro Asn Ile Arg Asn Thr Asp Gly Lys Ser Ala Leu Asp
305 310 315 320

Leu Ala Asp Pro Ser Ala Lys Ala Val Leu Thr Gly Glu Tyr Lys Lys
325 330 335

Asp Glu Leu Leu Glu Ala Ala Arg Ser Gly Asn Glu Glu Lys Leu Met
340 345 350

Ala Leu Leu Thr Pro Leu Asn Val Asn Cys His Ala Ser Asp Gly Arg
355 360 365

Lys Ser Thr Pro Leu His Leu Ala Ala Gly Tyr Asn Arg Val Arg Ile
370 375 380

Val Gln Leu Leu Leu Gln His Gly Ala Asp Val His Ala Lys Asp Lys
385 390 395 400

Gly Gly Leu Val Pro Leu His Asn Ala Cys Ser Tyr Gly His Tyr Glu
405 410 415

Val Thr Glu Leu Leu Leu Lys His Gly Ala Cys Val Asn Ala Met Asp
420 425 430

Leu Trp Gln Phe Thr Pro Leu His Glu Ala Ala Ser Lys Asn Arg Val
435 440 445

Glu Val Cys Ser Leu Leu Leu Ser His Gly Ala Asp Pro Thr Leu Val
450 455 460

Asn Cys His Gly Lys Ser Ala Val Asp Met Ala Pro Thr Pro Glu Leu
465 470 475 480

Arg Glu Arg Leu Thr Tyr Glu Phe Lys Gly His Ser Leu Leu Gln Ala
485 490 495

Ala Arg Glu Ala Asp Leu Ala Lys Val Lys Lys Thr Leu Ala Leu Glu
500 505 510

Ile Ile Asn Phe Lys Gln Pro Gln Ser His Glu Thr Ala Leu His Cys
515 520 525

Ala Val Ala Ser Leu His Pro Lys Arg Lys Gln Val Thr Glu Leu Leu
530 535 540

Leu Arg Lys Gly Ala Asn Val Asn Glu Lys Asn Lys Asp Phe Met Thr
545 550 555 560

Pro Leu His Val Ala Ala Glu Arg Ala His Asn Asp Val Met Glu Val
565 570 575

Leu His Lys His Gly Ala Lys Met Asn Ala Leu Asp Thr Leu Gly Gln
580 585 590

Thr Ala Leu His Arg Ala Ala Leu Ala Gly His Leu Gln Thr Cys Arg
595 600 605

Leu Leu Leu Ser Tyr Gly Ser Asp Pro Ser Ile Ile Ser Leu Gln Gly
610 615 620

Phe Thr Ala Ala Gln Met Gly Asn Glu Ala Val Gln Gln Ile Leu Ser
625 630 635 640

Glu Ser Thr Pro Ile Arg Thr Ser Asp Val Asp Tyr Arg Leu Leu Glu
645 650 655

Ala Ser Lys Ala Gly Asp Leu Glu Thr Val Lys Gln Leu Cys Ser Ser
660 665 670

Gln Asn Val Asn Cys Arg Asp Leu Glu Gly Arg His Ser Thr Pro Leu
675 680 685

His Phe Ala Ala Gly Tyr Asn Arg Val Ser Val Val Glu Tyr Leu Leu
690 695 700

His His Gly Ala Asp Val His Ala Lys Asp Lys Gly Gly Leu Val Pro
705 710 715 720

Leu His Asn Ala Cys Ser Tyr Gly His Tyr Glu Val Ala Glu Leu Leu
725 730 735

Val Arg His Gly Ala Ser Val Asn Val Ala Asp Leu Trp Lys Phe Thr
740 745 750

Pro Leu His Glu Ala Ala Ala Lys Gly Lys Tyr Glu Ile Cys Lys Leu
755 760 765

Leu Leu Lys His Gly Ala Asp Pro Thr Lys Lys Asn Arg Asp Gly Asn

770 775 780

Thr Pro Leu Asp Leu Val Lys Glu Gly Asp Thr Asp Ile Gln Asp Leu
785 790 795 800

Leu Lys Gly Asp Ala Ala Leu Leu Asp Ala Ala Lys Lys Gly Cys Leu
805 810 815

Ala Arg Val Gln Lys Leu Cys Thr Pro Glu Asn Ile Asn Cys Arg Asp
820 825 830

Thr Gln Gly Arg Asn Ser Thr Pro Leu His Leu Ala Ala Gly Tyr Asn
835 840 845

Asn Leu Glu Val Ala Glu Tyr Leu Leu Glu His Gly Ala Asp Val Asn
850 855 860

Ala Gln Asp Lys Gly Gly Leu Ile Pro Leu His Asn Ala Ala Ser Tyr
865 870 875 880

Gly His Val Asp Ile Ala Ala Leu Leu Ile Lys Tyr Asn Thr Cys Val
885 890 895

Asn Ala Thr Asp Lys Trp Ala Phe Thr Pro Leu His Glu Ala Ala Gln
900 905 910

Lys Gly Arg Thr Gln Leu Cys Ala Leu Leu Leu Ala His Gly Ala Asp
915 920 925

Pro Thr Met Lys Asn Gln Glu Gly Gln Thr Pro Leu Asp Leu Ala Thr
930 935 940

Ala Asp Asp Ile Arg Ala Leu Leu Ile Asp Ala Met Pro Pro Glu Ala
945 950 955 960

Leu Pro Thr Cys Phe Lys Pro Gln Ala Thr Val Val Ser Ala Ser Leu
965 970 975

Ile Ser Pro Ala Ser Thr Pro Ser Cys Leu Ser Ala Ala Ser Ser Ile
980 985 990

Asp Asn Leu Thr Gly Pro Leu Ala Glu Leu Ala Val Gly Gly Ala Ser
995 1000 1005

Asn Ala Gly Asp Gly Ala Ala Gly Thr Glu Arg Lys Glu Gly Glu
1010 1015 1020

Val Ala Gly Leu Asp Met Asn Ile Ser Gln Phe Leu Lys Ser Leu
1025 1030 1035

Gly Leu Glu His Leu Arg Asp Ile Phe Glu Thr Glu Gln Ile Thr
1040 1045 1050

Leu Asp Val Leu Ala Asp Met Gly His Glu Glu Leu Lys Glu Ile
1055 1060 1065

Gly Ile Asn Ala Tyr Gly His Arg His Lys Leu Ile Lys Gly Val
1070 1075 1080

Glu Arg Leu Leu Gly Gly Gln Gln Gly Thr Asn Pro Tyr Leu Thr
1085 1090 1095

Phe His Cys Val Asn Gln Gly Thr Ile Leu Leu Asp Leu Ala Pro
1100 1105 1110

Glu Asp Lys Glu Tyr Gln Ser Val Glu Glu Glu Met Gln Ser Thr
1115 1120 1125

Ile Arg Glu His Arg Asp Gly Gly Asn Ala Gly Gly Ile Phe Asn
1130 1135 1140

Arg Tyr Asn Val Ile Arg Ile Gln Lys Val Val Asn Lys Lys Leu
1145 1150 1155

Arg Glu Arg Phe Cys His Arg Gln Lys Glu Val Ser Glu Glu Asn
1160 1165 1170

His Asn His His Asn Glu Arg Met Leu Phe His Gly Ser Pro Phe
1175 1180 1185

Ile Asn Ala Ile Ile His Lys Gly Phe Asp Glu Arg His Ala Tyr
1190 1195 1200

Ile Gly Gly Met Phe Gly Ala Gly Ile Tyr Phe Ala Glu Asn Ser
1205 1210 1215

Ser Lys Ser Asn Gln Tyr Val Tyr Gly Ile Gly Gly Gly Thr Gly
1220 1225 1230

Cys Pro Thr His Lys Asp Arg Ser Cys Tyr Ile Cys His Arg Gln
1235 1240 1245

Met Leu Phe Cys Arg Val Thr Leu Gly Lys Ser Phe Leu Gln Phe

1250 1255 1260

Ser Thr Met Lys Met Ala His Ala Pro Pro Gly His His Ser Val
1265 1270 1275

Ile Gly Arg Pro Ser Val Asn Gly Leu Ala Tyr Ala Glu Tyr Val
1280 1285 1290

Ile Tyr Arg Gly Glu Gln Ala Tyr Pro Glu Tyr Leu Ile Thr Tyr
1295 1300 1305

Gln Ile Met Lys Pro Glu Ala Pro Ser Gln Thr Ala Thr Ala Ala
1310 1315 1320

Glu Gln Lys Thr
1325

<210> 50
<211> 1166
<212> PRT
<213> Homo sapiens

<400> 50

Met Ser Gly Arg Arg Cys Ala Gly Gly Gly Ala Ala Cys Ala Ser Ala
1 5 10 15

Ala Ala Glu Ala Val Glu Pro Ala Ala Arg Glu Leu Phe Glu Ala Cys
20 25 30

Arg Asn Gly Asp Val Glu Arg Val Lys Arg Leu Val Thr Pro Glu Lys
35 40 45

Val Asn Ser Arg Asp Thr Ala Gly Arg Lys Ser Thr Pro Leu His Phe
50 55 60

Ala Ala Gly Phe Gly Arg Lys Asp Val Val Glu Tyr Leu Leu Gln Asn
65 70 75 80

Gly Ala Asn Val Gln Ala Arg Asp Asp Gly Gly Leu Ile Pro Leu His
85 90 95

Asn Ala Cys Ser Phe Gly His Ala Glu Val Val Asn Leu Leu Leu Arg
100 105 110

His Gly Ala Asp Pro Asn Ala Arg Asp Asn Trp Asn Tyr Thr Pro Leu
115 120 125

His Glu Ala Ala Ile Lys Gly Lys Ile Asp Val Cys Ile Val Leu Leu
130 135 140

Gln His Gly Ala Glu Pro Thr Ile Arg Asn Thr Asp Gly Arg Thr Ala
145 150 155 160

Leu Asp Leu Ala Asp Pro Ser Ala Lys Ala Val Leu Thr Gly Glu Tyr
165 170 175

Lys Lys Asp Glu Leu Leu Glu Ser Ala Arg Ser Gly Asn Glu Glu Lys
180 185 190

Met Met Ala Leu Leu Thr Pro Leu Asn Val Asn Cys His Ala Ser Asp
195 200 205

Gly Arg Lys Ser Thr Pro Leu His Leu Ala Ala Gly Tyr Asn Arg Val
210 215 220

Lys Ile Val Gln Leu Leu Leu Gln His Gly Ala Asp Val His Ala Lys
225 230 235 240

Asp Lys Gly Asp Leu Val Pro Leu His Asn Ala Cys Ser Tyr Gly His
245 250 255

Tyr Glu Val Thr Glu Leu Leu Val Lys His Gly Ala Cys Val Asn Ala
260 265 270

Met Asp Leu Trp Gln Phe Thr Pro Leu His Glu Ala Ala Ser Lys Asn
275 280 285

Arg Val Glu Val Cys Ser Leu Leu Leu Ser Tyr Gly Ala Asp Pro Thr
290 295 300

Leu Leu Asn Cys His Asn Lys Ser Ala Ile Asp Leu Ala Pro Thr Pro
305 310 315 320

Gln Leu Lys Glu Arg Leu Ala Tyr Glu Phe Lys Gly His Ser Leu Leu
325 330 335

Gln Ala Ala Arg Glu Ala Asp Val Thr Arg Ile Lys Lys His Leu Ser
340 345 350

Leu Glu Met Val Asn Phe Lys His Pro Gln Thr His Glu Thr Ala Leu
355 360 365

His Cys Ala Ala Ala Ser Pro Tyr Pro Lys Arg Lys Gln Ile Cys Glu
370 375 380

Leu Leu Leu Arg Lys Gly Ala Asn Ile Asn Glu Lys Thr Lys Glu Phe
385 390 395 400

Leu Thr Pro Leu His Val Ala Ser Glu Lys Ala His Asn Asp Val Val
405 410 415

Glu Val Val Val Lys His Glu Ala Lys Val Asn Ala Leu Asp Asn Leu
420 425 430

Gly Gln Thr Ser Leu His Arg Ala Ala Tyr Cys Gly His Leu Gln Thr
435 440 445

Cys Arg Leu Leu Leu Ser Tyr Gly Cys Asp Pro Asn Ile Ile Ser Leu
450 455 460

Gln Gly Phe Thr Ala Leu Gln Met Gly Asn Glu Asn Val Gln Gln Leu
465 470 475 480

Leu Gln Glu Gly Ile Ser Leu Gly Asn Ser Glu Ala Asp Arg Gln Leu
485 490 495

Leu Glu Ala Ala Lys Ala Gly Asp Val Glu Thr Val Lys Lys Leu Cys
500 505 510

Thr Val Gln Ser Val Asn Cys Arg Asp Ile Glu Gly Arg Gln Ser Thr
515 520 525

Pro Leu His Phe Ala Ala Gly Tyr Asn Arg Val Ser Val Val Glu Tyr
530 535 540

Leu Leu Gln His Gly Ala Asp Val His Ala Lys Asp Lys Gly Gly Leu
545 550 555 560

Val Pro Leu His Asn Ala Cys Ser Tyr Gly His Tyr Glu Val Ala Glu
565 570 575

Leu Leu Val Lys His Gly Ala Val Val Asn Val Ala Asp Leu Trp Lys
580 585 590

Phe Thr Pro Leu His Glu Ala Ala Ala Lys Gly Lys Tyr Glu Ile Cys
595 600 605

Lys Leu Leu Leu Gln His Gly Ala Asp Pro Thr Lys Lys Asn Arg Asp
610 615 620

Gly Asn Thr Pro Leu Asp Leu Val Lys Asp Gly Asp Thr Asp Ile Gln
625   630   635   640

Asp Leu Leu Arg Gly Asp Ala Ala Leu Leu Asp Ala Ala Lys Lys Gly
                645   650   655

Cys Leu Ala Arg Val Lys Lys Leu Ser Ser Pro Asp Asn Val Asn Cys
            660   665   670

Arg Asp Thr Gln Gly Arg His Ser Thr Pro Leu His Leu Ala Ala Gly
        675   680   685

Tyr Asn Asn Leu Glu Val Ala Glu Tyr Leu Leu Gln His Gly Ala Asp
    690   695   700

Val Asn Ala Gln Asp Lys Gly Gly Leu Ile Pro Leu His Asn Ala Ala
705   710   715   720

Ser Tyr Gly His Val Asp Val Ala Ala Leu Leu Ile Lys Tyr Asn Ala
                725   730   735

Cys Val Asn Ala Thr Asp Lys Trp Ala Phe Thr Pro Leu His Glu Ala
            740   745   750

Ala Gln Lys Gly Arg Thr Gln Leu Cys Ala Leu Leu Leu Ala His Gly
        755   760   765

Ala Asp Pro Thr Leu Lys Asn Gln Glu Gly Gln Thr Pro Leu Asp Leu
    770   775   780

Val Ser Ala Asp Asp Val Ser Ala Leu Leu Thr Ala Ala Met Pro Pro
785   790   795   800

Ser Ala Leu Pro Ser Cys Tyr Lys Pro Gln Val Leu Asn Gly Val Arg
                805   810   815

Ser Pro Gly Ala Thr Ala Asp Ala Leu Ser Ser Gly Pro Ser Ser Pro
            820   825   830

Ser Ser Leu Ser Ala Ala Ser Ser Leu Asp Asn Leu Ser Gly Ser Phe
        835   840   845

Ser Glu Leu Ser Ser Val Val Ser Ser Ser Gly Thr Glu Gly Ala Ser
    850   855   860

Ser Leu Glu Lys Lys Glu Val Pro Gly Val Asp Phe Ser Ile Thr Gln
865   870   875   880

Phe Val Arg Asn Leu Gly Leu Glu His Leu Met Asp Ile Phe Glu Arg
885 890 895

Glu Gln Ile Thr Leu Asp Val Leu Val Glu Met Gly His Lys Glu Leu
900 905 910

Lys Glu Ile Gly Ile Asn Ala Tyr Gly His Arg His Lys Leu Ile Lys
915 920 925

Gly Val Glu Arg Leu Ile Ser Gly Gln Gln Gly Leu Asn Pro Tyr Leu
930 935 940

Thr Leu Asn Thr Ser Gly Ser Gly Thr Ile Leu Ile Asp Leu Ser Pro
945 950 955 960

Asp Asp Lys Glu Phe Gln Ser Val Glu Glu Glu Met Gln Ser Thr Val
965 970 975

Arg Glu His Arg Asp Gly Gly His Ala Gly Gly Ile Phe Asn Arg Tyr
980 985 990

Asn Ile Leu Lys Ile Gln Lys Val Cys Asn Lys Lys Leu Trp Glu Arg
995 1000 1005

Tyr Thr His Arg Arg Lys Glu Val Ser Glu Glu Asn His Asn His
1010 1015 1020

Ala Asn Glu Arg Met Leu Phe His Gly Ser Pro Phe Val Asn Ala
1025 1030 1035

Ile Ile His Lys Gly Phe Asp Glu Arg His Ala Tyr Ile Gly Gly
1040 1045 1050

Met Phe Gly Ala Gly Ile Tyr Phe Ala Glu Asn Ser Ser Lys Ser
1055 1060 1065

Asn Gln Tyr Val Tyr Gly Ile Gly Gly Gly Thr Gly Cys Pro Val
1070 1075 1080

His Lys Asp Arg Ser Cys Tyr Ile Cys His Arg Gln Leu Leu Phe
1085 1090 1095

Cys Arg Val Thr Leu Gly Lys Ser Phe Leu Gln Phe Ser Ala Met
1100 1105 1110

Lys Met Ala His Ser Pro Pro Gly His His Ser Val Thr Gly Arg
1115 1120 1125

Pro Ser Val Asn Gly Leu Ala Leu Ala Glu Tyr Val Ile Tyr Arg
1130 1135 1140

Gly Glu Gln Ala Tyr Pro Glu Tyr Leu Ile Thr Tyr Gln Ile Met
1145 1150 1155

Arg Pro Glu Gly Met Val Asp Gly
1160 1165

<210> 51
<211> 1243
<212> PRT
<213> Homo sapiens

<400> 51

Met Ser Glu Ala Pro Arg Phe Phe Val Gly Pro Glu Asp Thr Glu Ile
1 5 10 15

Asn Pro Gly Asn Tyr Arg His Phe Phe His His Ala Asp Glu Asp Asp
20 25 30

Glu Glu Glu Asp Asp Ser Pro Pro Glu Arg Gln Ile Val Val Gly Ile
35 40 45

Cys Ser Met Ala Lys Lys Ser Lys Ser Lys Pro Met Lys Glu Ile Leu
50 55 60

Glu Arg Ile Ser Leu Phe Lys Tyr Ile Thr Val Val Val Phe Glu Glu
65 70 75 80

Glu Val Ile Leu Asn Glu Pro Val Glu Asn Trp Pro Leu Cys Asp Cys
85 90 95

Leu Ile Ser Phe His Ser Lys Gly Phe Pro Leu Asp Lys Ala Val Ala
100 105 110

Tyr Ala Lys Leu Arg Asn Pro Phe Val Ile Asn Asp Leu Asn Met Gln
115 120 125

Tyr Leu Ile Gln Asp Arg Arg Glu Val Tyr Ser Ile Leu Gln Ala Glu
130 135 140

Gly Ile Leu Leu Pro Arg Tyr Ala Ile Leu Asn Arg Asp Pro Asn Asn
145 150 155 160

Pro Lys Glu Cys Asn Leu Ile Glu Gly Glu Asp His Val Glu Val Asn
165 170 175

Gly Glu Val Phe Gln Lys Pro Phe Val Glu Lys Pro Val Ser Ala Glu
180 185 190

Asp His Asn Val Tyr Ile Tyr Tyr Pro Thr Ser Ala Gly Gly Gly Ser
195 200 205

Gln Arg Leu Phe Arg Lys Ile Gly Ser Arg Ser Ser Val Tyr Ser Pro
210 215 220

Glu Ser Asn Val Arg Lys Thr Gly Ser Tyr Ile Tyr Glu Glu Phe Met
225 230 235 240

Pro Thr Asp Gly Thr Asp Val Lys Val Tyr Thr Val Gly Pro Asp Tyr
245 250 255

Ala His Ala Glu Ala Arg Lys Ser Pro Ala Leu Asp Gly Lys Val Glu
260 265 270

Arg Asp Ser Glu Gly Lys Glu Val Arg Tyr Pro Val Ile Leu Asn Ala
275 280 285

Arg Glu Lys Leu Ile Ala Trp Lys Val Cys Leu Ala Phe Lys Gln Thr
290 295 300

Val Cys Gly Phe Asp Leu Leu Arg Ala Asn Gly Gln Ser Tyr Val Cys
305 310 315 320

Asp Val Asn Gly Phe Ser Phe Val Lys Asn Ser Met Lys Tyr Tyr Asp
325 330 335

Asp Cys Ala Lys Ile Leu Gly Asn Ile Val Met Arg Glu Leu Ala Pro
340 345 350

Gln Phe His Ile Pro Trp Ser Ile Pro Leu Glu Ala Glu Asp Ile Pro
355 360 365

Ile Val Pro Thr Thr Ser Gly Thr Met Met Glu Leu Arg Cys Val Ile
370 375 380

Ala Val Ile Arg His Gly Asp Arg Thr Pro Lys Gln Lys Met Lys Met
385 390 395 400

Glu Val Arg His Gln Lys Phe Phe Asp Leu Phe Glu Lys Cys Asp Gly

405 410 415

Tyr Lys Ser Gly Lys Leu Lys Leu Lys Lys Pro Lys Gln Leu Gln Glu
420 425 430

Val Leu Asp Ile Ala Arg Gln Leu Leu Met Glu Leu Gly Gln Asn Asn
435 440 445

Asp Ser Glu Ile Glu Glu Asn Lys Pro Lys Leu Glu Gln Leu Lys Thr
450 455 460

Val Leu Glu Met Tyr Gly His Phe Ser Gly Ile Asn Arg Lys Val Gln
465 470 475 480

Leu Thr Tyr Leu Pro His Gly Cys Pro Lys Thr Ser Ser Glu Glu Glu
485 490 495

Asp Ser Arg Arg Glu Glu Pro Ser Leu Leu Leu Val Leu Lys Trp Gly
500 505 510

Gly Glu Leu Thr Pro Ala Gly Arg Val Gln Ala Glu Glu Leu Gly Arg
515 520 525

Ala Phe Arg Cys Met Tyr Pro Gly Gly Gln Gly Asp Tyr Ala Gly Phe
530 535 540

Pro Gly Cys Gly Leu Leu Arg Leu His Ser Thr Tyr Arg His Asp Leu
545 550 555 560

Lys Ile Tyr Ala Ser Asp Glu Gly Arg Val Gln Met Thr Ala Ala Ala
565 570 575

Phe Ala Lys Gly Leu Leu Ala Leu Glu Gly Glu Leu Thr Pro Ile Leu
580 585 590

Val Gln Met Val Lys Ser Ala Asn Met Asn Gly Leu Leu Asp Ser Asp
595 600 605

Ser Asp Ser Leu Ser Ser Cys Gln Gln Arg Val Lys Ala Arg Leu His
610 615 620

Glu Ile Leu Gln Lys Asp Arg Asp Phe Thr Ala Glu Asp Tyr Glu Lys
625 630 635 640

Leu Thr Pro Ser Gly Ser Ile Ser Leu Ile Lys Ser Met His Leu Ile
645 650 655

Lys Asn Pro Val Lys Thr Cys Asp Lys Val Tyr Ser Leu Ile Gln Ser
660 665 670

Leu Thr Ser Gln Ile Arg His Arg Met Glu Asp Pro Lys Ser Ser Asp
675 680 685

Ile Gln Leu Tyr His Ser Glu Thr Leu Glu Leu Met Leu Arg Arg Trp
690 695 700

Ser Lys Leu Glu Lys Asp Phe Lys Thr Lys Asn Gly Arg Tyr Asp Ile
705 710 715 720

Ser Lys Ile Pro Asp Ile Tyr Asp Cys Ile Lys Tyr Asp Val Gln His
725 730 735

Asn Gly Ser Leu Lys Leu Glu Asn Thr Met Glu Leu Tyr Arg Leu Ser
740 745 750

Lys Ala Leu Ala Asp Ile Val Ile Pro Gln Glu Tyr Gly Ile Thr Lys
755 760 765

Ala Glu Lys Leu Glu Ile Ala Lys Gly Tyr Cys Thr Pro Leu Val Arg
770 775 780

Lys Ile Arg Ser Asp Leu Gln Arg Thr Gln Asp Asp Asp Thr Val Asn
785 790 795 800

Lys Leu His Pro Val Tyr Ser Arg Gly Val Leu Ser Pro Glu Arg His
805 810 815

Val Arg Thr Arg Leu Tyr Phe Thr Ser Glu Ser His Val His Ser Leu
820 825 830

Leu Ser Ile Leu Arg Tyr Gly Ala Leu Cys Asn Glu Ser Lys Asp Glu
835 840 845

Gln Trp Lys Arg Ala Met Asp Tyr Leu Asn Val Val Asn Glu Leu Asn
850 855 860

Tyr Met Thr Gln Ile Val Ile Met Leu Tyr Glu Asp Pro Asn Lys Asp
865 870 875 880

Leu Ser Ser Glu Glu Arg Phe His Val Glu Leu His Phe Ser Pro Gly
885 890 895

Ala Lys Gly Cys Glu Glu Asp Lys Asn Leu Pro Ser Gly Tyr Gly Tyr

900 905 910

Arg Pro Ala Ser Arg Glu Asn Glu Gly Arg Arg Pro Phe Lys Ile Asp
915 920 925

Asn Asp Asp Glu Pro His Thr Ser Lys Arg Asp Glu Val Asp Arg Ala
930 935 940

Val Ile Leu Phe Lys Pro Met Val Ser Glu Pro Ile His Ile His Arg
945 950 955 960

Lys Ser Pro Leu Pro Arg Ser Arg Lys Thr Ala Thr Asn Asp Glu Glu
965 970 975

Ser Pro Leu Ser Val Ser Ser Pro Glu Gly Thr Gly Thr Trp Leu His
980 985 990

Tyr Thr Ser Gly Val Gly Thr Gly Arg Arg Arg Arg Arg Ser Gly Glu
995 1000 1005

Gln Ile Thr Ser Ser Pro Val Ser Pro Lys Ser Leu Ala Phe Thr
1010 1015 1020

Ser Ser Ile Phe Gly Ser Trp Gln Gln Val Val Ser Glu Asn Ala
1025 1030 1035

Asn Tyr Leu Arg Thr Pro Arg Thr Leu Val Glu Gln Lys Gln Asn
1040 1045 1050

Pro Thr Val Gly Ser His Cys Ala Gly Leu Phe Ser Thr Ser Val
1055 1060 1065

Leu Gly Gly Ser Ser Ser Ala Pro Asn Leu Gln Asp Tyr Ala Arg
1070 1075 1080

Thr His Arg Lys Lys Leu Thr Ser Ser Gly Cys Ile Asp Asp Ala
1085 1090 1095

Thr Arg Gly Ser Ala Val Lys Arg Phe Ser Ile Ser Phe Ala Arg
1100 1105 1110

His Pro Thr Asn Gly Phe Glu Leu Tyr Ser Met Val Pro Ser Ile
1115 1120 1125

Cys Pro Leu Glu Thr Leu His Asn Ala Leu Ser Leu Lys Gln Val
1130 1135 1140

Asp Glu Phe Leu Ala Ser Ile Ala Ser Pro Ser Ser Asp Val Pro
1145 1150 1155

Arg Lys Thr Ala Glu Ile Ser Ser Thr Ala Leu Arg Ser Ser Pro
1160 1165 1170

Ile Met Arg Lys Lys Val Ser Leu Asn Thr Tyr Thr Pro Ala Lys
1175 1180 1185

Ile Leu Pro Thr Pro Pro Ala Thr Leu Lys Ser Thr Lys Ala Ser
1190 1195 1200

Ser Lys Pro Ala Thr Ser Gly Pro Ser Ser Ala Val Val Pro Asn
1205 1210 1215

Thr Ser Ser Arg Lys Lys Asn Ile Thr Ser Lys Thr Glu Thr His
1220 1225 1230

Glu His Lys Lys Asn Thr Gly Lys Lys Lys
1235 1240

<210> 52
<211> 1406
<212> PRT
<213> Homo sapiens

<400> 52

Met Trp Ser Leu Thr Ala Ser Glu Gly Glu Ser Thr Thr Ala His Phe
1 5 10 15

Phe Leu Gly Ala Gly Asp Glu Gly Leu Gly Thr Arg Gly Ile Gly Met
20 25 30

Arg Pro Glu Glu Ser Asp Ser Glu Leu Leu Glu Asp Glu Glu Asp Glu
35 40 45

Val Pro Pro Glu Pro Gln Ile Ile Val Gly Ile Cys Ala Met Thr Lys
50 55 60

Lys Ser Lys Ser Lys Pro Met Thr Gln Ile Leu Glu Arg Leu Cys Arg
65 70 75 80

Phe Asp Tyr Leu Thr Val Val Ile Leu Gly Glu Asp Val Ile Leu Asn
85 90 95

Glu Pro Val Glu Asn Trp Pro Ser Cys His Cys Leu Ile Ser Phe His
100 105 110

Ser Lys Gly Phe Pro Leu Asp Lys Ala Val Ala Tyr Ser Lys Leu Arg
        115   120   125

Asn Pro Phe Leu Ile Asn Asp Leu Ala Met Gln Tyr Tyr Ile Gln Asp
    130   135   140

Arg Arg Glu Val Tyr Arg Ile Leu Gln Glu Glu Gly Ile Asp Leu Pro
145   150   155   160

Arg Tyr Ala Val Leu Asn Arg Asp Pro Ala Arg Pro Glu Glu Cys Asn
                165   170   175

Leu Ile Glu Gly Glu Asp Gln Val Glu Val Asn Gly Ala Val Phe Pro
            180   185   190

Lys Pro Phe Val Glu Lys Pro Val Ser Ala Glu Asp His Asn Val Tyr
        195   200   205

Ile Tyr Tyr Pro Ser Ser Ala Gly Gly Gly Ser Gln Arg Leu Phe Arg
    210   215   220

Lys Ile Gly Ser Arg Ser Ser Val Tyr Ser Pro Glu Ser Ser Val Arg
225   230   235   240

Lys Thr Gly Ser Tyr Ile Tyr Glu Glu Phe Met Pro Thr Asp Gly Thr
                245   250   255

Asp Val Lys Val Tyr Thr Val Gly Pro Asp Tyr Ala His Ala Glu Ala
            260   265   270

Arg Lys Ser Pro Ala Leu Asp Gly Lys Val Glu Arg Asp Ser Glu Gly
        275   280   285

Lys Glu Ile Arg Tyr Pro Val Met Leu Thr Ala Met Glu Lys Leu Val
    290   295   300

Ala Arg Lys Val Cys Val Ala Phe Lys Gln Thr Val Cys Gly Phe Asp
305   310   315   320

Leu Leu Arg Ala Asn Gly His Ser Phe Val Cys Asp Val Asn Gly Phe
                325   330   335

Ser Phe Val Lys Asn Ser Met Lys Tyr Tyr Asp Asp Cys Ala Lys Ile
            340   345   350

Leu Gly Asn Thr Ile Met Arg Glu Leu Ala Pro Gln Phe Gln Ile Pro
355 360 365

Trp Ser Ile Pro Thr Glu Ala Glu Asp Ile Pro Ile Val Pro Thr Thr
370 375 380

Ser Gly Thr Met Met Glu Leu Arg Cys Val Ile Ala Ile Ile Arg His
385 390 395 400

Gly Asp Arg Thr Pro Lys Gln Lys Met Lys Met Glu Val Lys His Pro
405 410 415

Arg Phe Phe Ala Leu Phe Glu Lys His Gly Gly Tyr Lys Thr Gly Lys
420 425 430

Leu Lys Leu Lys Arg Pro Glu Gln Leu Gln Glu Val Leu Asp Ile Thr
435 440 445

Arg Leu Leu Leu Ala Glu Leu Glu Lys Glu Pro Gly Gly Glu Ile Glu
450 455 460

Glu Lys Thr Gly Lys Leu Glu Gln Leu Lys Ser Val Leu Glu Met Tyr
465 470 475 480

Gly His Phe Ser Gly Ile Asn Arg Lys Val Gln Leu Thr Tyr Tyr Pro
485 490 495

His Gly Val Lys Ala Ser Asn Glu Gly Gln Asp Pro Gln Arg Glu Thr
500 505 510

Leu Ala Pro Ser Leu Leu Leu Val Leu Lys Trp Gly Gly Glu Leu Thr
515 520 525

Pro Ala Gly Arg Val Gln Ala Glu Glu Leu Gly Arg Ala Phe Arg Cys
530 535 540

Met Tyr Pro Gly Gly Gln Gly Asp Tyr Ala Gly Phe Pro Gly Cys Gly
545 550 555 560

Leu Leu Arg Leu His Ser Thr Phe Arg His Asp Leu Lys Ile Tyr Ala
565 570 575

Ser Asp Glu Gly Arg Val Gln Met Thr Ala Ala Ala Phe Ala Lys Gly
580 585 590

Leu Leu Ala Leu Glu Gly Glu Leu Thr Pro Ile Leu Val Gln Met Val
595 600 605

Lys Ser Ala Asn Met Asn Gly Leu Leu Asp Ser Asp Gly Asp Ser Leu
610 615 620

Ser Ser Cys Gln His Arg Val Lys Ala Arg Leu His His Ile Leu Gln
625 630 635 640

Gln Asp Ala Pro Phe Gly Pro Glu Asp Tyr Asp Gln Leu Ala Pro Thr
645 650 655

Arg Ser Thr Ser Leu Leu Asn Ser Met Thr Ile Ile Gln Asn Pro Val
660 665 670

Lys Val Cys Asp Gln Val Phe Ala Leu Ile Glu Asn Leu Thr His Gln
675 680 685

Ile Arg Glu Arg Met Gln Asp Pro Arg Ser Val Asp Leu Gln Leu Tyr
690 695 700

His Ser Glu Thr Leu Glu Leu Met Leu Gln Arg Trp Ser Lys Leu Glu
705 710 715 720

Arg Asp Phe Arg Gln Lys Ser Gly Arg Tyr Asp Ile Ser Lys Ile Pro
725 730 735

Asp Ile Tyr Asp Cys Val Lys Tyr Asp Val Gln His Asn Gly Ser Leu
740 745 750

Gly Leu Gln Gly Thr Ala Glu Leu Leu Arg Leu Ser Lys Ala Leu Ala
755 760 765

Asp Val Val Ile Pro Gln Glu Tyr Gly Ile Ser Arg Glu Glu Lys Leu
770 775 780

Glu Ile Ala Val Gly Phe Cys Leu Pro Leu Leu Arg Lys Ile Leu Leu
785 790 795 800

Asp Leu Gln Arg Thr His Glu Asp Glu Ser Val Asn Lys Leu His Pro
805 810 815

Leu Tyr Ser Arg Gly Val Leu Ser Pro Gly Arg His Val Arg Thr Arg
820 825 830

Leu Tyr Phe Thr Ser Glu Ser His Val His Ser Leu Leu Ser Val Phe
835 840 845

Arg Tyr Gly Gly Leu Leu Asp Glu Thr Gln Asp Ala Gln Trp Gln Arg
850 855 860

Ala Leu Asp Tyr Leu Ser Ala Ile Ser Glu Leu Asn Tyr Met Thr Gln
865 870 875 880

Ile Val Ile Met Leu Tyr Glu Asp Asn Thr Gln Asp Pro Leu Ser Glu
885 890 895

Glu Arg Phe His Val Glu Leu His Phe Ser Pro Gly Val Lys Gly Val
900 905 910

Glu Glu Glu Gly Ser Ala Pro Ala Gly Cys Gly Phe Arg Pro Ala Ser
915 920 925

Ser Glu Asn Glu Glu Met Lys Thr Asn Gln Gly Ser Met Glu Asn Leu
930 935 940

Cys Pro Gly Lys Ala Ser Asp Glu Pro Asp Arg Ala Leu Gln Thr Ser
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Pro Gln Pro Pro Glu Gly Pro Gly Leu Pro Arg Arg Ser Pro Leu Ile
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Arg Asn Arg Lys Ala Gly Ser Met Glu Val Leu Ser Glu Thr Ser Ser
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Ser Arg Pro Gly Gly Tyr Arg Leu Phe Ser Ser Ser Arg Pro Pro Thr
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Pro Thr Ile Tyr Pro Leu Glu Thr Leu His Asn Ala Leu Ser Leu
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Arg Gln Val Ser Glu Phe Leu Ser Arg Val Cys Gln Arg His Thr
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Asp Ala Gln Ala Gln Ala Ser Ala Ala Leu Phe Asp Ser Met His
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Ser Ser Gln Ala Ser Asp Asn Pro Phe Ser Pro Pro Arg Thr Leu
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His Ser Pro Pro Leu Gln Leu Gln Gln Arg Ser Glu Lys Pro Pro
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Trp Leu Glu Thr Arg Phe Cys His Val Gly Gln Ala Gly Leu Glu
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Leu Leu Thr Ser Ser Asp Leu Pro Ala Ser Ala Ser Gln Ser Ala
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Gly Ile Thr Gly Val Ser His Arg Thr Gln Pro Asp Ser Ser Gly
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Pro Ser Ser Thr Val Ser Ser Ala Gly Pro Ser Ser Pro Thr Thr
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Val Asp Gly Asn Ser Gln Phe Gly Phe Ser Asp Gln Pro Ser Leu
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Asn Ser His Val Ala Glu Glu His Gln Gly Leu Gly Leu Leu Gln
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Glu Thr Pro Gly Ser Gly Ala Gln Glu Leu Ser Ile Glu Gly Glu
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Glu Thr Ser Gln Pro Tyr Glu Glu Val Ser Gln Pro Cys Gln Glu
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Val Pro Asp Ile Ser Gln Pro Cys Gln Asp Ile Ser Glu Ala Leu
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Ser Gln Pro Cys Gln Lys Val Pro Asp Ile Ser Gln Gln Cys Gln
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Glu Asn His Asp Asn Gly Asn His Thr Cys Gln Glu Val Pro His
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Ile Ser Gln Pro Cys Gln Lys Ser Ser Gln Leu Cys Gln Lys Val
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Ser Gln Pro Cys Gln Gly Val Ser Val Glu Val Gly Lys Leu Val
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Gln Pro Tyr Gln Glu Phe Ser Val Glu Val Gly Arg Leu Ala Gln
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Glu Thr Ser Ala Ile Asn Leu Leu Ser Gln Gly Ile Pro Glu Ile
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Pro Leu Asp Pro Lys Leu Leu Glu Asp Leu Val Gln Pro Pro Thr Ile
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Thr Gln Gln Ser Pro Lys Asp Tyr Ile Ile Asp Pro Arg Glu Asn Ile
    50                  55                  60

Val Ile Gln Cys Glu Ala Lys Gly Lys Pro Pro Pro Ser Phe Ser Trp
65                  70                  75                  80

Thr Arg Asn Gly Thr His Phe Asp Ile Asp Lys Asp Pro Leu Val Thr
                85                  90                  95

Met Lys Pro Gly Thr Gly Thr Leu Ile Ile Asn Ile Met Ser Glu Gly
            100                 105                 110

Lys Ala Glu Thr Tyr Glu Gly Val Tyr Gln Cys Thr Ala Arg Asn Glu
        115                 120                 125

Arg Gly Ala Ala Val Ser Asn Asn Ile Val Val Arg Pro Ser Arg Ser
    130                 135                 140

Pro Leu Trp Thr Lys Glu Lys Leu Glu Pro Ile Thr Leu Gln Ser Gly
145                 150                 155                 160

Gln Ser Leu Val Leu Pro Cys Arg Pro Pro Ile Gly Leu Pro Pro Pro
                165                 170                 175

Ile Ile Phe Trp Met Asp Asn Ser Phe Gln Arg Leu Pro Gln Ser Glu
            180                 185                 190

Arg Val Ser Gln Gly Leu Asn Gly Asp Leu Tyr Phe Ser Asn Val Leu
        195                 200                 205

Pro Glu Asp Thr Arg Glu Asp Tyr Ile Cys Tyr Ala Arg Phe Asn His
    210                 215                 220

Thr Gln Thr Ile Gln Gln Lys Gln Pro Ile Ser Val Lys Val Ile Ser
225                 230                 235                 240

Ala Lys Ser Ser Arg Glu Arg Pro Pro Thr Phe Leu Thr Pro Glu Gly
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Asn Ala Ser Asn Lys Glu Glu Leu Arg Gly Asn Val Leu Ser Leu Glu
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Cys Ile Ala Glu Gly Leu Pro Thr Pro Ile Ile Tyr Trp Ala Lys Glu
275 280 285

Asp Gly Met Leu Pro Lys Asn Arg Thr Val Tyr Lys Asn Phe Glu Lys
290 295 300

Thr Leu Gln Ile Ile His Val Ser Glu Ala Asp Ser Gly Asn Tyr Gln
305 310 315 320

Cys Ile Ala Lys Asn Ala Leu Gly Ala Ile His His Thr Ile Ser Val
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Arg Val Lys Ala Ala Pro Tyr Trp Ile Thr Ala Pro Gln Asn Leu Val
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Leu Ser Pro Gly Glu Asp Gly Thr Leu Ile Cys Arg Ala Asn Gly Asn
355 360 365

Pro Lys Pro Arg Ile Ser Trp Leu Thr Asn Gly Val Pro Ile Glu Ile
370 375 380

Ala Pro Asp Asp Pro Ser Arg Lys Ile Asp Gly Asp Thr Ile Ile Phe
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Ser Asn Val Gln Glu Arg Ser Ser Ala Val Tyr Gln Cys Asn Ala Ser
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Asn Glu Tyr Gly Tyr Leu Leu Ala Asn Ala Phe Val Asn Val Leu Ala
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Glu Pro Pro Arg Ile Leu Thr Pro Ala Asn Thr Leu Tyr Gln Val Ile
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Ala Asn Arg Pro Ala Leu Leu Asp Cys Ala Phe Phe Gly Ser Pro Leu
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Pro Thr Ile Glu Trp Phe Lys Gly Ala Lys Gly Ser Ala Leu His Glu
465 470 475 480

Asp Ile Tyr Val Leu His Glu Asn Gly Thr Leu Glu Ile Pro Val Ala
485 490 495

Gln Lys Asp Ser Thr Gly Thr Tyr Thr Cys Val Ala Arg Asn Lys Leu
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Gly Met Ala Lys Asn Glu Val His Leu Glu Ile Lys Asp Ala Thr Trp
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Ile Val Lys Gln Pro Glu Tyr Ala Val Val Gln Arg Gly Ser Met Val
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Ser Phe Glu Cys Lys Val Lys His Asp His Thr Leu Ser Leu Thr Val
545   550   555   560

Leu Trp Leu Lys Asp Asn Arg Glu Leu Pro Ser Asp Glu Arg Phe Thr
                565   570   575

Val Asp Lys Asp His Leu Val Val Ala Asp Val Ser Asp Asp Asp Ser
            580   585   590

Gly Thr Tyr Thr Cys Val Ala Asn Thr Thr Leu Asp Ser Val Ser Ala
        595   600   605

Ser Ala Val Leu Ser Val Val Ala Pro Thr Pro Thr Pro Ala Pro Val
    610   615   620

Tyr Asp Val Pro Asn Pro Pro Phe Asp Leu Glu Leu Thr Asp Gln Leu
625   630   635   640

Asp Lys Ser Val Gln Leu Ser Trp Thr Pro Gly Asp Asp Asn Asn Ser
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Pro Ile Thr Lys Phe Ile Ile Glu Tyr Glu Asp Ala Met His Lys Pro
            660   665   670

Gly Leu Trp His His Gln Thr Glu Val Ser Gly Thr Gln Thr Thr Ala
        675   680   685

Gln Leu Asn Leu Ser Pro Tyr Val Asn Tyr Ser Phe Arg Val Met Ala
    690   695   700

Val Asn Ser Ile Gly Lys Ser Leu Pro Ser Glu Ala Ser Glu Gln Tyr
705   710   715   720

Leu Thr Lys Ala Ser Glu Pro Asp Lys Asn Pro Thr Ala Val Glu Gly
                725   730   735

Leu Gly Ser Glu Pro Asp Asn Leu Val Ile Thr Trp Lys Pro Leu Asn
            740   745   750

Gly Phe Glu Ser Asn Gly Pro Gly Leu Gln Tyr Lys Val Ser Trp Arg
755 760 765

Gln Lys Asp Gly Asp Asp Glu Trp Thr Ser Val Val Val Ala Asn Val
770 775 780

Ser Lys Tyr Ile Val Ser Gly Thr Pro Thr Phe Val Pro Tyr Leu Ile
785 790 795 800

Lys Val Gln Ala Leu Asn Asp Met Gly Phe Ala Pro Glu Pro Ala Val
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Val Met Gly His Ser Gly Glu Asp Leu Pro Met Val Ala Pro Gly Asn
820 825 830

Val Arg Val Asn Val Val Asn Ser Thr Leu Ala Glu Val His Trp Asp
835 840 845

Pro Val Pro Leu Lys Ser Ile Arg Gly His Leu Gln Gly Tyr Arg Ile
850 855 860

Tyr Tyr Trp Lys Thr Gln Ser Ser Ser Lys Arg Asn Arg Arg His Ile
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Glu Lys Lys Ile Leu Thr Phe Gln Gly Ser Lys Thr His Gly Met Leu
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Pro Gly Leu Glu Pro Phe Ser His Tyr Thr Leu Asn Val Arg Val Val
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Asn Gly Lys Gly Glu Gly Pro Ala Ser Pro Asp Arg Val Phe Asn Thr
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Pro Glu Gly Val Pro Ser Ala Pro Ser Ser Leu Lys Ile Val Asn Pro
930 935 940

Thr Leu Asp Ser Leu Thr Leu Glu Trp Asp Pro Pro Ser His Pro Asn
945 950 955 960

Gly Ile Leu Thr Glu Tyr Thr Leu Lys Tyr Gln Pro Ile Asn Ser Thr
965 970 975

His Glu Leu Gly Pro Leu Val Asp Leu Lys Ile Pro Ala Asn Lys Thr
980 985 990

Arg Trp Thr Leu Lys Asn Leu Asn Phe Ser Thr Arg Tyr Lys Phe Tyr
995 1000 1005

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Glu Pro Ala Glu Gly Asn Glu Ser Ser Glu Ala Pro Ser Pro Val
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Asn Ala Met Asn Ser Phe Val
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